

Reference Example 156

To a mixture of 3-benzyloxy-4-ethoxybenzyl alcohol (4.80 g), acetone cyanohydrin (3.50 g), triphenylphosphine (9.86 g) and tetrahydrofuran (100 ml) was dropwise added a 40% toluene solution (16.16 g) of diethyl azodicarboxylate at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-4-ethoxyphenyl)acetonitrile (3.68 g, yield 74%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 1.47 (3H, t, J=6.8 Hz), 3.67 (2H, s), 4.12 (2H, q, J=6.8 Hz), 5.15 (2H, s), 6.74-6.96 (3H, m), 7.28-7.47 (5H, m).

15 Reference Example 157

A mixture of (3-benzyloxy-4-ethoxyphenyl)acetonitrile (3.68 g), 4N aqueous sodium hydroxide solution (10 ml) and ethanol (50 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (5 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. A mixture of the residue, a 10% solution (20 ml) of hydrochloric acid in methanol and methanol (50 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-4-ethoxyphenyl)acetate (2.99 g, yield 72%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 1.45 (3H, t, J=7.0 Hz), 3.54 (2H, s), 3.69 (3H, s), 4.11 (2H, q, J=7.0 Hz), 5.13 (2H, s), 6.70-6.88 (3H,

m), 7.27-7.48 (5H, m).

Reference Example 158

A mixture of methyl (3-benzyloxy-4-ethoxyphenyl)acetate (2.99 g), 5% palladium-carbon (0.61 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (4-ethoxy-3-hydroxyphenyl)acetate (1.89 g, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 1.44 (3H, t, J=7.0 Hz), 3.54 (2H, s), 3.69 (3H, s), 4.11 (2H, q, J=7.0 Hz), 5.61 (1H, s), 6.72-6.89 (3H, m).

15 Reference Example 159

A mixture of 3-fluorosalicylaldehyde (5.20 g), benzyl bromide (4.5 ml), potassium carbonate (5.26 g) and N,N-dimethylformamide (75 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-fluorobenzaldehyde (8.24 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 5.28 (2H, s), 7.07-7.16 (1H, m), 7.24-7.42 (6H, m), 7.56-7.60 (1H, m), 10.25 (1H, s).

Reference Example 160

To a solution of 2-benzyloxy-3-fluorobenzaldehyde (8.24 g) in tetrahydrofuran (50 ml) was added lithium aluminum hydride (0.45 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (4.02 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by

filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-fluorobenzyl alcohol (8.18 g, yield 98%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

¹H-NMR (CDCl₃)δ: 1.87 (1H, t, J=6.6 Hz), 4.58 (2H, d, J=6.6 Hz), 5.17 (2H, s), 6.97-7.13 (3H, m), 7.34-7.46 (5H, m).

Reference Example 161

To a mixture of 2-benzyloxy-3-fluorobenzyl alcohol (8.10 g), acetone cyanohydrin (4.95 g), triphenylphosphine (18.57 g) and tetrahydrofuran (150 ml) was dropwise added a 40% solution (30.36 g) of diethyl azodicarboxylate in toluene at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-fluorophenylacetonitrile (7.20 g, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 3.56 (2H, s), 5.19 (2H, s), 6.98-7.18 (3H, m), 7.30-7.46 (5H, m).

Reference Example 162

A mixture of 2-benzyloxy-3-fluorophenylacetonitrile (7.20 g), 4N aqueous sodium hydroxide solution (10 ml) and ethanol (50 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (4 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. A mixture of the residue, a 10% solution (50 ml) of hydrochloric acid in methanol and methanol (50 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel

column chromatography, and methyl (2-benzyloxy-3-fluorophenyl)acetate (6.63 g, yield 81%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 3.62 (5H, s), 5.12 (2H, s), 6.94-7.12 (3H, m), 7.26-7.47 (5H, m).

Reference Example 163

A mixture of methyl (2-benzyloxy-3-fluorophenyl)acetate (6.63 g), 5% palladium-carbon (1.44 g) and tetrahydrofuran (150 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-fluoro-2-hydroxyphenyl)acetate (4.53 g, yield 98%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.58 (1H, br t), 3.71 (2H, s), 3.74 (3H, s), 6.74-7.08 (3H, m).

Reference Example 164

15 A mixture of [1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]methanol (2.00 g), activated manganese dioxide (6.08 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazole-4-carbaldehyde (1.84 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.

20 melting point: 69-70°C.

Reference Example 165

To a mixture of 1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazole-4-carbaldehyde (1.50 g), ethyl diethylphosphonoacetate (1.62 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.27 g) at 0°C and

the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-[1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propenoate (1.83 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

Reference Example 166

A mixture of 2-ethylbutanoic acid (7.03 g), 1,1'-carbonyldiimidazole (10.30 g) and tetrahydrofuran (200 ml) was refluxed for 1.5 hours. After cooling to room temperature, magnesium chloride (6.66 g) and potassium ethyl malonate (11.90 g) were added and the mixture was refluxed for 1.5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the residue and N,N-dimethylformamide dimethyl acetal (15.00 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (100 ml), and a solution of hydrazine monohydrate (3.03 g) in ethanol (30 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (9.83 g, yield 77%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

¹H-NMR (CDCl₃) δ : 0.85 (6H, t, J=7.0 Hz), 1.36 (3H, t, J=7.0 Hz), 1.50-1.88 (4H, m), 3.28-3.50 (1H, m), 4.29 (2H, q, J=7.0 Hz), 7.96 (1H, s).

Reference Example 167

5 A mixture of ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (5.00 g), 2-chloro-5-(trifluoromethyl)pyridine (4.35 g), potassium carbonate (4.84 g) and N,N-dimethylformamide (75 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (7.45
15 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃) δ : 0.88 (6H, t, J=7.2 Hz), 1.38 (3H, t, J=7.0 Hz), 1.60-1.95 (4H, m), 3.20-3.40 (1H, m), 4.32 (2H, q, J=7.0 Hz), 7.98-8.17 (2H, m), 8.65-8.70 (1H, m), 8.99 (1H, s).

20 **Reference Example 168**

To a solution of ethyl 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (6.58 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (40 ml) of diisobutylaluminum hydride in hexane at
25 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was
30 subjected to silica gel column chromatography, and {3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (5.16 g, yield 89%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

35 ¹H-NMR (CDCl₃) δ : 0.88 (6H, t, J=7.4 Hz), 1.42 (1H, t, J=5.2

Hz), 1.66–1.88 (4H, m), 2.60–2.80 (1H, m), 4.64 (2H, d, J=5.2 Hz), 7.93–8.11 (2H, m), 8.50 (1H, s), 8.61–8.65 (1H, m).

Reference Example 169

A mixture of {3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (5.00 g), activated manganese dioxide (15.18 g) and tetrahydrofuran (50 mL) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (4.75 g, yield 95%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 0.88 (6H, t, J=7.4 Hz), 1.68–1.94 (4H, m), 3.08–3.20 (1H, m), 8.02–8.17 (2H, m), 8.67–8.72 (1H, m), 9.03 (1H, s), 10.03 (1H, s).

Reference Example 170

To a mixture of 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (4.70 g), ethyl diethylphosphonoacetate (4.06 g) and N,N-dimethylformamide (50 mL) was added sodium hydride (60%, in oil, 0.66 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (5.45 g, yield 95%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 0.88 (6H, t, J=7.4 Hz), 1.34 (3H, t, J=7.0 Hz), 1.66–1.90 (4H, m), 2.70–2.88 (1H, m), 4.26 (2H, q, J=7.0 Hz), 6.30 (1H, d, J=16.0 Hz), 7.61 (1H, d, J=16.0 Hz), 7.97–8.14 (2H, m), 8.62–8.69 (1H, m), 8.78 (1H, s).

Reference Example 171

A mixture of ethyl (E)-3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (5.45 g), 5% palladium-carbon (1.02 g) and tetrahydrofuran (50 ml)
5 was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate
10 (5.28 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).
¹H-NMR (CDCl₃)δ: 0.87 (6H, t, J=7.2 Hz), 1.27 (3H, t, J=7.0 Hz), 1.64-1.86 (4H, m), 2.51-2.68 (3H, m), 2.76-2.88 (2H, m), 4.16 (2H, q, J=7.0 Hz), 7.90-8.07 (2H, m), 8.29 (1H, s), 8.58-
15 8.62 (1H, m).

Reference Example 172

To a solution of ethyl 3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate (5.20 g) in tetrahydrofuran (30 ml) was dropwise added a 1.0 M
20 solution (30 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
25 solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (4.29 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane
30 (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 79-80°C.

Reference Example 173

A mixture of 2-methylbutanoic acid (10.27 g), 1,1'-carbonyldimidazole (16.48 g) and tetrahydrofuran (200 ml) was
35 refluxed for 1.5 hours. After cooling to room temperature,

magnesium chloride (10.58 g) and potassium ethyl malonate (18.92 g) were added and the mixture was refluxed for 1.5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. A mixture of the residue and N,N-dimethylformamide dimethyl acetal (18.05 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (150 ml) and a solution of hydrazine monohydrate (5.13 g) in ethanol (50 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylpropyl)-1H-pyrazole-4-carboxylate (14.48 g, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (3H, t, $J=7.2$ Hz), 1.31 (3H, d, $J=7.2$ Hz), 1.36 (3H, t, $J=7.2$ Hz), 1.50-1.82 (2H, m), 3.44-3.58 (1H, m), 4.29 (2H, q, $J=7.2$ Hz), 7.94 (1H, s).

Reference Example 174

A mixture of ethyl 3-(1-methylpropyl)-1H-pyrazole-4-carboxylate (10.00 g), 2-chloro-5-(trifluoromethyl)pyridine (9.38 g), potassium carbonate (8.66 g) and N,N-dimethylformamide (100 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (15.39 g, yield 88%) was obtained as colorless crystals from a

fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 63-64°C.

Reference Example 175

5 To a solution of ethyl 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (13.44 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (90 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1
10 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and {3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (10.86 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 76-77°C.

20 **Reference Example 176**

A mixture of {3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (8.00 g), activated manganese dioxide (24.16 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material 25 was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.39 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized 30 from ethyl acetate-hexane. melting point: 82-83°C.

Reference Example 177

To a mixture of 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (6.50 g), ethyl diethylphosphonoacetate (5.06 g) and N,N-

dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 0.88 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was 5 washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.59 10 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 75-76°C.

Reference Example 178

15 A mixture of ethyl (E)-3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.30 g), 5% palladium-carbon (1.48 g) and tetrahydrofuran (50 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the 20 filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.21 g, yield 98%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).
25 1H -NMR ($CDCl_3$) δ : 0.92 (3H, t, $J=7.2$ Hz), 1.20-1.34 (6H, m), 1.54-1.90 (2H, m), 2.58-2.68 (2H, m), 2.76-2.87 (3H, m), 4.16 (2H, q, $J=7.2$ Hz), 7.90-8.05 (2H, m), 8.28 (1H, s), 8.57-8.63 (1H, m).

Reference Example 179

30 To a solution of ethyl 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.20 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (50 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 35 hour. The reaction mixture was poured into dilute hydrochloric

acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (6.09 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 72-73°C.

10 **Reference Example 180**

A mixture of 2-methylpentanoic acid (11.65 g), 1,1'-carbonyldiimidazole (17.89 g) and tetrahydrofuran (200 ml) was refluxed for 1.5 hours. After cooling to room temperature, magnesium chloride (10.48 g) and potassium 15 ethoxycarbonylacetate (18.75 g) were added and the mixture was refluxed for 1.5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and 20 concentrated. A mixture of the residue and N,N-dimethylformamide dimethylacetal (17.90 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (200 ml), and a solution of hydrazine monohydrate (5.10 g) in ethanol (50 ml) was slowly added at 25 room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue 30 was subjected to silica gel column chromatography, and ethyl 3-(1-methylbutyl)-1H-pyrazole-4-carboxylate (16.85 g, yield 80%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

¹H-NMR (CDCl_3) δ : 0.90 (3H, t, $J=7.0$ Hz), 1.18-1.44 (6H, m), 35 1.48-1.80 (4H, m), 3.52-3.70 (1H, m), 4.30 (2H, q, $J=7.0$ Hz),

7.94 (1H, s).

Reference Example 181

A mixture of ethyl 3-(1-methylbutyl)-1H-pyrazole-4-carboxylate (6.50 g), 2-chloro-5-(trifluoromethyl)pyridine⁵ (5.85 g), potassium carbonate (5.09 g) and N,N-dimethylformamide (100 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried¹⁰ (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (9.71 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).¹⁵

¹⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (3H, t, $J=7.2$ Hz), 1.23-1.92 (10H, m), 3.44-3.59 (1H, m), 4.32 (2H, q, $J=7.2$ Hz), 8.00-8.15 (2H, m), 8.65-8.69 (1H, m), 8.97 (1H, s).

Reference Example 182

To a solution of ethyl 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (9.71 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (60 ml) of diisobutyl aluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric²⁵ acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and {3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (8.21 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).³⁰

¹⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (3H, t, $J=6.8$ Hz), 1.27-1.90 (8H, m), 2.88-3.10 (1H, m), 4.65 (2H, d, $J=6.2$ Hz), 7.93-8.10 (2H, m), 35 8.48 (1H, s), 8.60-8.66 (1H, m).

Reference Example 183

A mixture of {3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (8.21 g), activated manganese dioxide (26.48 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.56 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 63-64°C.

Reference Example 184

To a mixture of 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.40 g), ethyl diethylphosphonoacetate (5.50 g) and N,N-dimethylformamide (70 ml) was added sodium hydride (60%, in oil, 0.96 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (8.15 g, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

1H -NMR ($CDCl_3$) δ : 0.92 (3H, t, $J=7.2$ Hz), 1.24-1.45 (8H, m), 1.56-1.88 (2H, m), 2.98-3.14 (1H, m), 4.27 (2H, q, $J=7.2$ Hz), 6.29 (1H, d, $J=16.2$ Hz), 7.62 (1H, d, $J=16.2$ Hz), 7.98-8.13 (2H, m), 8.64-8.70 (1H, m), 8.76 (1H, s).

Reference Example 185

A mixture of ethyl (E)-3-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (8.15 g), 5% palladium-carbon (1.33 g) and tetrahydrofuran (75 ml)

was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (8.10 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).
10 $^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (3H, t, $J=7.4$ Hz), 1.22-1.90 (10H, m), 2.58-2.68 (2H, m), 2.76-2.98 (3H, m), 4.16 (2H, q, $J=7.0$ Hz), 7.90-8.06 (2H, m), 8.28 (1H, s), 8.58-8.63 (1H, m).

Reference Example 186

To a solution of ethyl 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (8.10 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M
15 solution (50 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
20 solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (6.63 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane
25 (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 72-73°C.

Reference Example 187

To a solution of 3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (0.90 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.17 g) at 0°C and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-5-(trifluoromethyl)pyridine (0.93 g) was added at room temperature and the mixture was stirred overnight at 50°C. The
35 reaction mixture was poured into water, and extracted with

ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.59 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (6H, d, $J=7.0$ Hz), 1.88-2.00 (2H, m), 2.55-2.66 (2H, m), 2.97-3.15 (1H, m), 3.38 (3H, s), 3.58-3.67 (2H, m), 4.65 (2H, s), 8.01 (1H, s), 8.02-8.09 (1H, m), 8.57-8.61 (1H, m).

Reference Example 188

A mixture of 1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.59 g), conc. hydrochloric acid (0.05 ml) and methanol (50 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl)-1-propanol (1.33 g, yield 94%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 66-67°C.

Reference Example 189

To a solution of 3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (0.98 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.19 g) at 0°C and the mixture was stirred at room temperature for 15 minutes. 2,5-Dibromopyridine (1.15 g) was added at room temperature, and the mixture was stirred overnight at 100°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 1-(5-bromo-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.63 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.32 (6H, d, $J=7.0$ Hz), 1.84-2.02 (2H, m), 2.52-2.64 (2H, m), 2.94-3.10 (1H, m), 3.38 (3H, s), 3.55-3.66 (2H, m), 4.65 (2H, s), 7.81-7.85 (2H, m), 8.19 (1H, s), 8.36-8.39 (1H, m).

Reference Example 190

A mixture of 1-(5-bromo-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.63 g), conc. hydrochloric acid (0.05 ml) and methanol (50 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-bromo-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (1.32 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

Reference Example 191

A mixture of ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (41.42 g), benzyl bromide (25 ml), potassium carbonate (30.00 g) and N,N-dimethylformamide (200 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 1-benzyl-3-(1-ethylpropyl)-1H-

pyrazole-4-carboxylate (55.62 g, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃) δ : 0.84 (6H, t, J=7.2 Hz), 1.31 (3H, t, J=7.2 Hz), 1.60-1.88 (4H, m), 3.14-3.32 (1H, m), 4.23 (2H, q, J=7.2 Hz), 5.27 (2H, s), 7.10-7.40 (5H, m), 7.86 (1H, s).

Reference Example 192

To a solution of ethyl 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (55.62 g) in tetrahydrofuran (200 ml)
10 was added lithium aluminum hydride (5.38 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (53.88 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the
15 filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]methanol (47.18 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

¹H-NMR (CDCl₃) δ : 0.84 (6H, t, J=7.4 Hz), 1.22 (1H, br t), 1.60-1.82 (4H, m), 2.48-2.70 (1H, m), 4.52 (2H, d, J=5.0 Hz), 5.26 (2H, s), 7.08-7.42 (6H, m).

Reference Example 193

A mixture of [1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]methanol (47.18 g), activated manganese dioxide (152.00 g)
25 and tetrahydrofuran (300 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carbaldehyde (42.25 g, yield 90%)
30 was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃) δ : 0.85 (6H, t, J=7.4 Hz), 1.67-1.90 (4H, m), 2.88-3.10 (1H, m), 5.29 (2H, s), 7.18-7.41 (5H, m), 7.76 (1H, s), 9.87 (1H, s).

35 **Reference Example 194**

To a mixture of 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carbaldehyde (42.25 g), ethyl diethylphosphonoacetate (40.70 g) and N,N-dimethylformamide (200 ml) was added sodium hydride (60%, in oil, 6.95 g) at 0°C and the mixture was stirred 5 overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica 10 gel column chromatography, and ethyl (E)-3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propenoate (52.30 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 0.83 (6H, t, J=7.2 Hz), 1.30 (3H, t, J=7.2 15 Hz), 1.60-1.84 (4H, m), 2.64-2.78 (1H, m), 4.21 (2H, q, J=7.2 Hz), 5.27 (2H, s), 6.02 (1H, d, J=15.6 Hz), 7.08-7.42 (5H, m), 7.51 (1H, s), 7.57 (1H, d, J=15.6 Hz).

Reference Example 195

A mixture of ethyl (E)-3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propenoate (10.00 g), 5% palladium-carbon (10.26 g), formic acid (50 ml) and ethanol (50 ml) was refluxed for 5 hours. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium chloride 25 solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-(1-ethylpropyl)-1H-pyrazol-4-yl]propionate (6.60 g, yield 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

¹H-NMR (CDCl₃)δ: 0.82 (6H, t, J=7.4 Hz), 1.25 (3H, t, J=7.4 30 Hz), 1.50-1.82 (4H, m), 2.48-2.81 (5H, m), 4.14 (2H, q, J=7.4 Hz), 7.36 (1H, s).

Reference Example 196

To a solution of 3-isopropyl-4-[3-35 (methoxymethoxy)propyl]-1H-pyrazole (0.90 g) in N,N-

dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.19 g) at 0°C, and the mixture was stirred at room temperature for 30 minutes. 2,3,5-Trichloropyridine (0.89 g) was added at room temperature, and the mixture was stirred at 5 room temperature for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 1-(3,5-dichloro-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-¹⁰ 1H-pyrazole (1.19 g, yield 78%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.34 (6H, d, $J=7$ Hz), 1.85-2.00 (2H, m), 2.55-¹⁵ 2.65 (2H, m), 2.95-3.15 (1H, m), 3.38 (3H, s), 3.62 (2H, t, $J=6$ Hz), 4.65 (2H, s), 7.84 (1H, s), 7.86 (1H, d, $J=2$ Hz), 8.35 (1H, d, $J=2$ Hz).

Reference Example 197

A mixture of 1-(3,5-dichloro-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.18 g), conc.²⁰ hydrochloric acid (0.1 ml) and methanol (20 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated to give 3-[1-(3,5-dichloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (1.02 g, yield 99%) as a colorless oil.²⁵

¹H-NMR ($CDCl_3$) δ : 1.34 (6H, d, $J=7$ Hz), 1.80-2.00 (2H, m), 2.55-³⁰ 2.65 (2H, m), 2.95-3.15 (1H, m), 3.70-3.80 (2H, m), 7.84 (1H, s), 7.86 (1H, d, $J=2$ Hz), 8.35 (1H, d, $J=2$ Hz).

Reference Example 198

To a mixture of sodium ethoxide (39.58 g) and diisopropyl ether (800 ml) was added a mixture of ethyl valerate (74.21 g) and ethyl formate (50.67 g) at 0°C over 1 hour. The mixture was stirred at room temperature overnight. Acetic acid (66 ml)³⁵

was added to the reaction mixture over 20 minutes and then hydrazine monohydrate (32.0 g) was added over 10 minutes. The mixture was refluxed for 2 hours. Water (150 ml) was added to the reaction mixture and the mixture was stirred at 0°C for 1 hour. The precipitated crystals were collected by filtration, washed with cold water and isopropyl ether, and dried to give gray-white crystals. To a mixture of the obtained crystals, triethylamine (10.1 ml) and tetrahydrofuran (70 ml) was added di-tert-butyl dicarbonate (16.7 ml) and the mixture was stirred overnight at room temperature. The reaction solution was concentrated and water was added to the residue. The resulting crystals were collected by filtration, washed with water and hexane, and dried to give tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (10.30 g, yield 66%) as white crystals. melting point: 70-71°C (decomposition).

¹H-NMR (CDCl₃)δ: 0.95 (3H, t, J=7.3 Hz), 1.55-1.65 (11H, m), 2.35 (2H, t, J=7.4 Hz), 7.62 (1H, br s).

Reference Example 199

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (660 mg), tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (530 mg), tributylphosphine (860 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (1.06 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with diethyl ether-hexane (1:4, volume ratio). A mixture of the obtained oily substance and 4N hydrogen chloride ethyl acetate solution (10 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 4-propyl-3-(3-{3-propyl-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazole (700 mg, yield 79%). melting point: 127-128°C.

Reference Example 200

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (1.00 g), tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (790 mg), tributylphosphine (1.31 g) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.64 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance and 4N hydrogen chloride ethyl acetate solution (20 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-propyl-1H-pyrazole (1.19 g, yield 89%). melting point: 121-122°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.94 (3H, t, $J= 7.3\text{Hz}$), 1.42 (3H, t, $J= 7.1\text{Hz}$), 1.57 (2H, sextet, $J= 7.4\text{Hz}$), 2.09 (2H, quintet, $J= 7.0\text{Hz}$), 2.34 (2H, t, $J= 7.4\text{Hz}$), 2.59 (2H, t, $J= 7.4\text{Hz}$), 4.24 (2H, t, $J= 6.3\text{Hz}$), 4.35 (2H, q, $J= 7.0\text{Hz}$), 7.14 (1H, s), 7.80 (1H, d, $J= 8.5\text{Hz}$), 7.90 (1H, dd, $J= 8.8, 2.2\text{Hz}$), 8.20 (1H, s), 8.53-8.55 (1H, m), 8.82 (1H, br s).

Reference Example 201

A mixture of cyclohexylhydrazine hydrochloride (20.12 g), dimethyl acetylenedicarboxylate (19.00 g), potassium acetate (13.11 g), acetic acid (70 ml) and toluene (70 ml) was stirred at 80°C for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. Toluene was added to the residue, and the resulting solid was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-cyclohexyl-3-hydroxy-1H-pyrazole-5-carboxylate (11.86 g, yield 40%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:6, volume ratio). melting point: 195-196°C.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.23-1.97 (10H, m), 3.87 (3H, s), 5.00-5.10 (1H, m), 6.14 (1H, s), 10.99 (1H, br s).

Reference Example 202

A mixture of methyl 1-cyclohexyl-3-hydroxy-1H-pyrazole-5-carboxylate (11.00 g), benzyl bromide (6.10 ml), potassium carbonate (6.80 g) and N,N-dimethylformamide (80 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-cyclohexyl-1H-pyrazole-5-carboxylate (15.40 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.18-1.48 (3H, m), 1.65-1.74 (1H, m), 1.82-1.97 (6H, m), 3.84 (3H, s), 4.94-5.03 (1H, m), 5.17 (2H, s), 6.18 (1H, s), 7.28-7.47 (5H, m).

Reference Example 203

To a mixture of lithium aluminum hydride (4.65 g) and 30 tetrahydrofuran (100 ml) was slowly added a solution of methyl 3-benzyloxy-1-cyclohexyl-1H-pyrazole-5-carboxylate (15.40 g) in tetrahydrofuran (10 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (13 ml) was added. The precipitate was removed by filtration

and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)methanol (13.61 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). melting point: 195-196°C.

¹H-NMR (CDCl₃)δ: 1.20-1.45 (3H, m), 1.55-1.73 (2H, m), 1.84-2.01 (6H, m), 3.97-4.07 (1H, m), 4.57 (2H, d, J= 6.1Hz), 5.15 (2H, s), 5.59 (1H, s), 7.27-7.47 (5H, m).

¹⁰ **Reference Example 204**

A mixture of (3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)methanol (12.50 g), activated manganese dioxide (50.0 g) and tetrahydrofuran (250 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (6.75 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 1.20 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)propenoate (7.72 g, yield 50%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

³⁰ ¹H-NMR (CDCl₃)δ: 1.17-1.49 (6H, m), 1.67-1.76 (1H, m), 1.83-2.02 (6H, m), 4.06-4.15 (1H, m), 4.26 (2H, q, J= 7.1Hz), 5.17 (2H, s), 5.92 (1H, s), 6.27 (1H, d, J= 15.9Hz), 7.28-7.47 (5H, m), 7.55 (1H, d, J= 15.9Hz).

Reference Example 205

³⁵ A mixture of ethyl (E)-3-(3-benzyloxy-1-cyclohexyl-1H-

pyrazol-5-yl)propanoate (7.70 g), 5% palladium-carbon (1.0 g), tetrahydrofuran (50 ml) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate 5 was concentrated to give ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (5.54 g, yield 96%) as colorless crystals. melting point: 173-174°C.

Reference Example 206

To a mixture of methyl acetylenedicarboxylate (29.20 g) 10 and methanol (200 ml) was added hydrazine monohydrate (10.30 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to give yellow crystals (28.61 g). To a mixture of the obtained crystals, triethylamine (29.5 ml) and tetrahydrofuran (200 ml) 15 was added di-tert-butyl dicarbonate (48.6 ml), and the mixture was stirred overnight. The reaction mixture was concentrated. A mixture of the obtained residue, benzyl bromide, potassium carbonate (29.20 g) and N,N-dimethylformamide (200 ml) was stirred overnight at room temperature. The reaction mixture 20 was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the residue and 4N hydrogen chloride ethyl acetate solution (100 ml) was stirred overnight 25 at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column 30 chromatography, and methyl 3-benzyloxy-1H-pyrazole-5-carboxylate (12.10 g, yield 26%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

1H -NMR ($CDCl_3$) δ : 3.89 (3H, s), 5.25 (2H, s), 6.26 (1H, s), 35 7.22-7.47 (5H, m), 10.60 (1H, br s).

Reference Example 207

To a mixture of methyl 3-benzyloxy-1H-pyrazole-5-carboxylate (12.10 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 1.20 g) at 0°C and the mixture was stirred for 30 minutes. Isopropyl iodide (5.70 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-(1-methylethyl)-1H-pyrazole-5-carboxylate (7.34 g, yield 51%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

15 ¹H-NMR (CDCl₃)δ: 1.44 (6H, d, J=6.6 Hz), 3.84 (3H, s), 5.18 (2H, s), 5.41 (1H, septet, J= 6.6Hz), 6.18 (1H, s), 7.27-7.47 (5H, m).

Reference Example 208

To a mixture of lithium aluminum hydride (1.30 g) and tetrahydrofuran (50 ml) was slowly added a solution of methyl 3-benzyloxy-1-(1-methylethyl)-1H-pyrazole-5-carboxylate (7.34 g) in tetrahydrofuran (5 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (4 ml) was further added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl]methanol (2.63 g, yield 40%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (2:3, volume ratio).

30 ¹H-NMR (CDCl₃)δ: 1.44 (6H, d, J= 6.6Hz), 1.74 (1H, t, J=6.1 Hz), 4.48 (1H, septet, J=6.6 Hz), 4.57 (2H, d, J= 5.8Hz), 5.15 (2H, s), 5.58 (1H, s), 7.24-7.50 (5H, m).

Reference Example 209

35 A mixture of [3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-

yl]methanol (2.60 g), activated manganese dioxide (8.0 g) and tetrahydrofuran (30 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected
5 to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (1.67 g) and N,N-dimethylformamide (20 ml) was added sodium hydride (60%, in
10 oil, 0.30 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica
15 gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propenoate (1.23 g, yield 37%) was obtained as a colorless oil from a fraction eluted with diethyl ether-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃)δ: 1.33 (3H, t, J= 7.1Hz), 1.46 (6H, d, J= 6.6Hz), 4.26 (2H, q, J= 7.2Hz), 4.57 (1H, septet, J= 6.6Hz), 5.17 (2H, s), 5.92 (1H, s), 6.27 (1H, d, J= 15.8Hz), 7.27-7.50 (5H, m), 7.54 (1H, d, J= 15.8Hz).

Reference Example 210

A mixture of ethyl (E)-3-(3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propenoate (1.23 g), 5% palladium-carbon (0.2 g) and tetrahydrofuran (10 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give ethyl 3-(3-hydroxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propanoate (0.88 g, quantitative) as colorless crystals. melting point: 123-124°C.

¹H-NMR (CDCl₃)δ: 1.27 (3H, t, J= 7.1Hz), 1.42 (6H, d, J= 6.6Hz), 2.57-2.68 (2H, m), 2.80-2.92 (2H, m), 4.16 (2H, q, J= 7.1Hz), 4.32 (1H, septet, J= 6.6Hz), 5.37 (1H, s).

35 Reference Example 211

A mixture of methyl 4-methyl-3-oxopentanoate (20.00 g) and 1,1-dimethoxytrimethylamine (24.8 g) was refluxed for 2 hours. The reaction mixture was concentrated to give a yellow oily substance. To a mixture of the obtained oily substance 5 and ethanol (200 ml) was added hydrazine monohydrate (7.30 g) at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and brine in this order, 10 dried ($MgSO_4$) and concentrated to give a brown oily substance. A mixture of the obtained oily substance, benzyl bromide (17.0 ml), potassium carbonate (20.0 g) and N,N-dimethylformamide (200 ml) was stirred at room temperature for 4 hours. The reaction mixture was poured into water, and extracted with 15 ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-benzyl-3-(1-methylethyl)-1H-pyrazole-4-carboxylate (29.93 g, yield 84%) was obtained as a 20 yellow oily substance from a fraction eluted with diethyl ether-hexane (1:4, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.31 (6H, d, $J=7.0Hz$), 3.30-3.60 (1H, m), 3.76 (3H, s), 5.24 (2H, s), 7.18-7.40 (5H, m), 7.69 (1H, s).

Reference Example 212

25 To a mixture of lithium aluminum hydride (5.50 g) and tetrahydrofuran (260 ml) was slowly added a solution of methyl 1-benzyl-3-(1-methylethyl)-1H-pyrazole-4-carboxylate (29.93 g) in tetrahydrofuran (40 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly 30 added to decompose excess lithium aluminum hydride and brine (15 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (25.21 g, yield 94%) was 35 obtained as a colorless oil from a fraction eluted with

acetone-hexane (2:3, volume ratio).

¹H-NMR (CDCl₃)δ: 1.32 (6H, d, J= 7.0Hz), 1.45 (1H, br s), 3.08 (1H, septet, J= 7.0Hz), 4.54 (2H, br s), 5.22 (2H, s), 7.14-7.40 (6H, m).

5 Reference Example 213

A mixture of [1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (25.00 g), activated manganese dioxide (100.0 g) and tetrahydrofuran (350 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (25.80 g) and N,N-dimethylformamide (180 ml) was added sodium hydride (60%, in oil, 4.60 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl)propenoate (30.25 g, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

²⁵ ¹H-NMR (CDCl₃)δ: 1.30 (3H, t, J= 7.3Hz), 1.33 (6H, d, J= 6.8Hz), 3.16 (1H, septet, J= 6.8Hz), 4.21 (2H, q, J= 7.2Hz), 5.25 (2H, s), 6.51 (1H, d, J= 16.0Hz), 7.18-7.40 (5H, m), 7.45 (1H, s), 7.58 (1H, d, J= 16.0Hz).

Reference Example 214

³⁰ To a mixture of 2-ethylphenol (12.22 g), tributylamine (7.41 g) and toluene (50 ml) was added tin tetrachloride (2.61 g) and the mixture was stirred at room temperature for 30 minutes. Paraformaldehyde (6.60 g) was added and the mixture was stirred overnight at 100°C. The reaction mixture was ³⁵ poured into dilute hydrochloric acid, and extracted with ethyl

acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-ethylsalicylaldehyde (8.20 g, yield 55%)
5 was obtained as a colorless oil from a fraction eluted with hexane.

1H -NMR ($CDCl_3$) δ : 1.23 (3H, t, $J=7.6$ Hz), 2.70 (2H, q, $J=7.6$ Hz), 6.96 (1H, t, $J=7.6$ Hz), 7.37-7.42 (2H, m), 9.89 (1H, s), 11.28 (1H, s).

10 Reference Example 215

To a mixture of lithium aluminum hydride (2.00 g) and tetrahydrofuran (50 ml) was slowly added a solution of ethyl 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (11.73 g) in tetrahydrofuran (10 ml) at 0°C, and the mixture
15 was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (5.5 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and
20 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (9.95 g, yield 98%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (2:3, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.29 (6H, d, $J= 7.0Hz$), 1.44 (1H, t, $J= 5.3Hz$), 1.70-1.85 (2H, m), 2.49 (2H, t, $J= 7.7Hz$), 2.98 (1H, septet, $J= 7.0Hz$), 3.67 (2H, d, $J= 5.9Hz$), 5.22 (2H, s), 7.02 (1H, s), 7.13-7.39 (5H, m).

Reference Example 216

To a mixture of 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (9.95 g), N-ethyldiisopropylamine (10.0 ml)
30 and tetrahydrofuran (100 ml) was added chloromethyl methyl ether (5.50 ml) at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
35 solution, dried ($MgSO_4$) and concentrated. The residue was

subjected to silica gel column chromatography, and 1-benzyl-4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (10.57 g, yield 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (6H, d, $J= 7.0\text{Hz}$), 1.70-1.88 (2H, m), 2.49 (2H, t, $J= 7.7\text{Hz}$), 2.98 (1H, septet, $J= 7.0\text{Hz}$), 3.34 (3H, s), 3.54 (2H, t, $J= 6.4\text{Hz}$), 4.61 (2H, s), 5.22 (2H, s), 7.01 (1H, s), 7.12-7.38 (5H, m).

Reference Example 217

10 A mixture of 1-benzyl-4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (10.57 g), 5% palladium-carbon (2.0 g) and tetrahydrofuran (100 ml) was stirred overnight at 50°C under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (7.44 g, quantitative) as a yellow oily substance.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (6H, d, $J= 7.0\text{Hz}$), 1.77-1.94 (2H, m), 2.53 (2H, t, $J= 7.7\text{Hz}$), 3.05 (1H, septet, $J= 7.0\text{Hz}$), 3.38 (3H, s), 3.57 (2H, t, $J= 6.4\text{Hz}$), 4.64 (2H, s), 7.34 (1H, s).

20 Reference Example 218

To a mixture of ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (1.00 g), 2-chloro-5-nitropyridine (0.79 g) and N,N-dimethylformamide (10 ml) was added sodium hydride (60%, in oil, 0.25 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propanoate (1.26 g, yield 74%) was obtained as yellow crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). melting point: 90-91°C.

30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J= 7.2\text{Hz}$), 1.34 (6H, d, $J= 7.0\text{Hz}$), 2.60-2.72 (2H, m), 2.78-2.90 (2H, m), 3.04 (1H,

septet, $J = 6.9\text{Hz}$), 4.17 (2H, q, $J = 7.2\text{Hz}$), 8.05 (1H, d, $J = 9.0\text{Hz}$), 8.30 (1H, s), 8.50 (1H, dd, $J = 9.2, 2.6\text{Hz}$), 9.20 (1H, dd, $J = 2.6, 0.6\text{Hz}$).

Reference Example 219

5 A mixture of ethyl 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propanoate (1.18 g), 5% palladium-carbon (0.15 g), methanol (4 ml) and tetrahydrofuran (4 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the
10 filtrate was concentrated to give ethyl 3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (0.93 g, yield 94%) as yellow crystals. melting point: 75–76°C.
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (3H, t, $J = 7.1\text{Hz}$), 1.32 (6H, d, $J = 6.9\text{Hz}$), 2.57–2.65 (2H, m), 2.77–2.85 (2H, m), 3.03 (1H,
15 septet, $J = 6.9\text{Hz}$), 3.63 (2H, br s), 4.14 (2H, q, $J = 7.2\text{Hz}$), 7.09 (1H, dd, $J = 8.9, 2.9\text{Hz}$), 7.70 (1H, dd, $J = 8.6, 0.8\text{Hz}$),
7.82 (1H, dd, $J = 3.0, 0.6\text{Hz}$), 8.09 (1H, s).

Reference Example 220

To a mixture of ethyl 3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (2.00 g), tetrafluoroboric acid (42%, 4 ml) and 1,4-dioxane (3 ml) was slowly added a solution of sodium nitrite (0.50 g) in water (1 ml) at 0°C and the mixture was stirred for 30 minutes. Cold water (30 ml) was added to the reaction mixture, and the
25 precipitated crystals were collected by filtration, washed with water and air-dried. The obtained crystal was slowly added to toluene (15 ml) heated to 90°C, and the mixture was stirred at 100°C for 30 minutes. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
30 chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance (1.17 g) was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). To a
35 mixture of the obtained oily substance and tetrahydrofuran (15

ml) was slowly added a 1.5M solution (6.5 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and
5 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-fluoro-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (0.74 g, yield 42%)
10 was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). melting point: 78-79°C.

1H -NMR ($CDCl_3$) δ : 1.32 (6H, d, $J= 6.9Hz$), 1.83-1.98 (2H, m),
2.58 (2H, t, $J= 7.8Hz$), 3.02 (1H, septet, $J= 6.9Hz$), 3.74 (2H,
15 t, $J= 5.6Hz$), 7.42-7.52 (1H, m), 7.88-7.95 (1H, m), 8.14-8.20 (2H, m).

Reference Example 221

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (0.50 g), 6-chloropyridine-3-carbonitrile (0.36 g) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 0.12 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at 80°C for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (2 drops) and methanol (6 ml) was stirred overnight at 60°C. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and the precipitated
25 crystals were collected by filtration, washed with water and dried to give 6-[4-(3-hydroxypropyl)-3-(1-methylethyl)-1H-pyrazol-1-yl]pyridine-3-carbonitrile (550 mg, yield 90%) as colorless crystals. melting point: 105-106°C.

1H -NMR ($CDCl_3$) δ : 1.32 (6H, d, $J= 7.0Hz$), 1.47 (1H, br s), 1.82-2.00 (2H, m), 2.53-2.66 (2H, m), 3.03 (1H, septet, $J= 6.9Hz$),

3.75 (2H, t, J= 6.4Hz), 7.95 (1H, dd, J= 8.6, 2.0Hz), 8.03 (1H, dd, J= 8.6, 1.0Hz), 8.25 (1H, t, J= 0.9Hz), 8.61 (1H, dd, J= 2.0, 1.0Hz).

Reference Example 222

5 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.50 g), 2-chloro-5-nitropyridine (1.23 g) and N,N-dimethylformamide (10 ml) was added sodium hydride (60%, in oil, 0.37 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at 80°C for 3
10 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (2 drops) and methanol (6 ml) was
15 stirred overnight at 60°C. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and the precipitated crystals were collected by filtration, washed with water and dried to give 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (1.60 g, yield 80%) as colorless
20 crystals. melting point: 130-131°C.

25 1H -NMR ($CDCl_3$) δ : 1.34 (6H, d, J= 7.0Hz), 1.36 (1H, t, J= 5.0Hz), 1.84-2.00 (2H, m), 2.55-2.67 (2H, m), 3.04 (1H, septet, J= 6.9Hz), 3.76 (2H, t, J= 6.0Hz), 8.06 (1H, d, J= 9.2Hz), 8.30 (1H, s), 8.51 (1H, dd, J= 9.2, 2.8Hz), 9.20 (1H, dd, J= 2.5, 0.7Hz).

Reference Example 223

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.52 g), 2-chloro-5-methylpyridine (1.83 g) and N,N-dimethylformamide (15 ml), was added sodium
30 hydride (60%, in oil, 0.43 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at 110°C overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained residue,

conc. hydrochloric acid (2 ml) and methanol (20 ml) was refluxed of 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
5 solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[3-(1-methylethyl)-1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (0.80 g, yield 43%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane
10 (2:3, volume ratio). melting point: 82-83°C.
 1H -NMR ($CDCl_3$) δ : 1.33 (6H, d, $J= 7.0\text{Hz}$), 1.56 (1H, br s), 1.82-1.97 (2H, m), 2.32 (3H, s), 2.58 (2H, t, $J= 7.7\text{Hz}$), 3.03 (1H, septet, $J= 7.0\text{Hz}$), 3.74 (2H, t, $J= 6.4\text{Hz}$), 7.52-7.60 (1H, m), 7.82 (1H, d, $J= 8.4\text{Hz}$), 8.14-8.16 (1H, m), 8.20 (1H, s).

15 **Reference Example 224**

To a mixture of 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (1.18 g), methyl (3-methoxy-2-hydroxyphenyl)acetate (800 mg), tributylphosphine (1.64 g) and tetrahydrofuran (40 ml) was added 1,1'-
20 azodicarbonyldipiperidine (2.05 g) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-methoxy-2-{3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate
25 (1.30 g, yield 50%) was obtained as yellow crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). melting point: 108-109°C.

1H -NMR ($CDCl_3$) δ : 1.35 (6H, d, $J= 7.0\text{Hz}$), 2.00-2.17 (2H, m), 2.71 (2H, t, $J= 7.7\text{Hz}$), 3.07 (1H, septet, $J= 6.9\text{Hz}$), 3.68 (3H, s), 3.85 (2H, s), 4.07 (2H, t, $J= 6.2\text{Hz}$), 6.80-6.90 (2H, m), 7.02 (1H, dd, $J= 8.4, 7.4\text{Hz}$), 8.06 (1H, d, $J= 9.2\text{Hz}$), 8.35 (1H, s), 8.51 (1H, dd, $J= 9.1, 2.5\text{Hz}$), 9.20 (1H, d, $J= 2.2\text{Hz}$).

Reference Example 225

A mixture of methyl (3-methoxy-2-{3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate
35

(0.88 g), 5% palladium-carbon (0.1 g), methanol (4 ml) and tetrahydrofuran (4 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-(3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetate (0.80 g, yield 95%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹⁰ ¹H-NMR (CDCl₃) δ: 1.33 (6H, d, J= 7.0Hz), 1.97-2.15 (2H, m), 2.68 (2H, t, J= 7.8Hz), 3.05 (1H, septet, J= 6.9Hz), 3.63 (2H, br s), 3.66 (3H, s), 3.68 (2H, s), 3.83 (3H, s), 4.06 (2H, t, J= 6.4Hz), 6.78-6.88 (2H, m), 6.95-7.27 (2H, m), 7.72 (1H, d, J= 8.8Hz), 7.83 (1H, d, J= 2.6Hz), 8.14 (1H, s).

¹⁵ **Reference Example 226**

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 3-chloro-6-(trifluoromethyl)pyridazine (1.03 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.28 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and ²⁰ methanol (15 ml) was refluxed for 4 hours. The reaction mixture was poured into ice water, and the precipitated crystals were collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and 3-(3-(1-methylethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)-1-propanol (1.00 g, yield 68%) was obtained as ³⁰ colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:3, volume ratio). melting point: 113-114°C.

¹H-NMR (CDCl₃) δ: 1.33 (6H, d, J= 6.6Hz), 1.42 (1H, t, J= 5.1Hz), 1.84-2.01 (2H, m), 2.63 (2H, t, J= 7.9Hz), 3.05 (1H, septet, J= 6.8Hz), 3.77 (2H, q, J= 5.7Hz), 7.83 (1H, d, J=

9.0Hz), 8.29 (1H, d, J= 9.0Hz), 8.50 (1H, s).

Reference Example 227

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 3-chloro-6-methoxypyridazine (0.82 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.24 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (15 ml) was refluxed for 4 hours. The reaction mixture was poured into ice water, and the precipitated crystals were collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and 3-(1-[6-methoxypyridazin-3-yl]-3-(1-methylethyl)-1H-pyrazol-4-yl)-1-propanol (300 mg, yield 23%) was obtained as a colorless oil from a fraction eluted with acetone-chloroform (1:4, volume ratio). melting point: 122-123°C.

²⁰ ¹H-NMR (CDCl₃)δ: 1.32 (6H, d, J= 6.9Hz), 1.39 (1H, t, J= 5.3Hz), 1.84-1.97 (2H, m), 2.60 (2H, t, J= 7.7Hz), 3.03 (1H, septet, J= 7.0Hz), 3.75 (2H, q, J= 5.8Hz), 4.12 (3H, s), 7.06 (1H, d, J= 9.3Hz), 8.11 (1H, d, J= 9.3Hz), 8.32 (1H, s).

Reference Example 228

²⁵ To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 6-chloropyridazine-3-carbonitrile (0.72 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.24 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (15 ml) was refluxed for 4 hours. The reaction mixture was poured into ice water, and the precipitated crystals were

collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and 6-[4-(3-hydroxypropyl)-3-(1-methylethyl)-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (950 mg, yield 74%) was obtained as colorless
5 crystals from a fraction eluted with ethyl acetate-chloroform (1:2, volume ratio). melting point: 140-141°C.

¹H-NMR (CDCl₃)δ: 1.32 (6H, d, J= 7.0Hz), 1.37 (1H, t, J= 5.1Hz), 1.84-2.01 (2H, m), 2.63 (2H, t, J= 7.9Hz), 3.05 (1H, septet, J= 6.9Hz), 3.77 (2H, q, J= 5.6Hz), 7.82 (1H, d, J= 10 9.0Hz), 8.25 (1H, d, J= 9.0Hz), 8.48-8.50 (1H, m).

Reference Example 229

To a mixture of 3-(1-ethylpropyl)-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (2.20 g), 3-chloro-6-(trifluoromethyl)pyridazine (2.17 g) and N,N-dimethylformamide
15 (30 ml) was added sodium hydride (60%, in oil, 0.48 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
20 chloride solution, dried (MgSO₄) and concentrated. A mixture of the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with
25 saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)-1-propanol (1.73 g, yield 55%) was obtained as colorless crystals from a
30 fraction eluted with ethyl acetate-hexane (1:2, volume ratio). melting point: 86-87°C.

¹H-NMR (CDCl₃)δ: 0.87 (6H, d, J= 7.3Hz), 1.46 (1H, br s), 1.60-2.00 (6H, m), 2.53-2.70 (3H, m), 3.76 (2H, t, J= 6.4Hz), 7.83 (1H, d, J= 9.2Hz), 8.29 (1H, d, J= 9.2Hz), 8.51 (1H, s).

35 Reference Example 230

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.50 g), 2-methylthio-5-(trifluoromethyl)pyrimidine (1.40 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.48 g) at 0°C, 5 and, after termination of hydrogen generation, the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture 10 of the obtained residue, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. 15 The residue was subjected to silica gel column chromatography, and 3-[3-(1-methylethyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl]-1-propanol (240 mg, yield 11%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:3, volume 20 ratio). melting point: 98-99°C.

1H -NMR ($CDCl_3$) δ : 1.38 (6H, d, $J= 7.0Hz$), 1.85-2.01 (2H, m), 2.63 (2H, t, $J= 7.7Hz$), 3.11 (1H, septet, $J= 7.0Hz$), 3.77 (2H, t, $J= 6.2Hz$), 8.34 (1H, s), 8.91 (2H, s).

Reference Example 231

25 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 2-methylthiopyrimidine-5-carbonitrile (0.80 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.24 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at 30 room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and 35 methanol (20 ml) was refluxed for 4 hours. The reaction

mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 2-[4-(3-hydroxypropyl)-3-(1-methylethyl)-1H-pyrazol-1-yl]pyrimidine-5-carbonitrile (450 mg, yield 36%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:4, volume ratio). melting point: 153-154°C.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (6H, d, $J= 7.0\text{Hz}$), 1.44 (1H, t, $J= 5.2\text{Hz}$), 1.84-2.00 (2H, m), 2.62 (2H, t, $J= 7.8\text{Hz}$), 3.10 (1H, septet, $J= 7.0\text{Hz}$), 3.77 (2H, q, $J= 5.9\text{Hz}$), 8.31 (1H, s), 8.93 (2H, s).

Reference Example 232

15 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.20 g), 2-chloro-5-ethylpyrimidine (0.89 g) and N,N-dimethylformamide (15 mL) was added sodium hydride (60%, in oil, 0.29 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (1 ml) and methanol (20 ml) was refluxed for 5 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-ethylpyrimidin-2-yl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (1.36 g, yield 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (7:3, volume ratio). melting point: 70-71°C.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J= 7.5\text{Hz}$), 1.37 (6H, d, $J= 6.8\text{Hz}$), 1.73 (1H, br s), 1.83-2.00 (2H, m), 2.54-2.72 (4H, m),

3.11 (1H, septet, $J= 7.0\text{Hz}$) , 3.75 (2H, t, $J= 6.4\text{Hz}$) , 8.28 (1H, s), 8.53 (2H, s).

Reference Example 233

To a mixture of 3-(1-ethylpropyl)-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (2.70 g), 2-methylthio-5-(trifluoromethyl)pyrimidine (2.62 g) and tetrahydrofuran (50 ml) was added sodium hydride (60%, in oil, 0.58 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 6 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl]-1-propanol (1.19 g, yield 31%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (6H, t, $J= 7.3\text{Hz}$) , 1.63-2.00 (6H, m), 2.55-2.80 (3H, m), 3.76 (2H, t, $J= 6.2\text{Hz}$) , 8.35 (1H, s), 8.92 (2H, s).

Reference Example 234

A mixture of methyl (2-hydroxy-3-methoxyphenyl)acetate (1.00 g), benzyl alcohol (1.10 g), p-toluenesulfonic acid monohydrate (0.10 g) and toluene (15 ml) was stirred overnight at 90°C while evaporating produced methanol. The reaction mixture was concentrated. The residue was subjected to silica gel column chromatography, and benzyl (2-hydroxy-3-methoxyphenyl)acetate (1.35 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane

(1:2, volume ratio).

¹H-NMR (CDCl₃)δ: 3.73 (2H, s), 3.88 (3H, s), 5.16 (2H, s), 5.87 (1H, s), 6.80 (3H, s), 7.28-7.40 (5H, m).

Reference Example 235

5 A mixture of ethyl 3-[3-(1-ethylpropyl)-1H-pyrazol-4-yl]propanoate (10.57 g), benzyl bromide (4.40 ml), potassium carbonate (5.00 g) and N,N-dimethylformamide (80 ml) was stirred at 70°C for 6 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl
10 acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). To a mixture of
15 lithium aluminum hydride (1.50 g) and tetrahydrofuran (20 ml) was slowly added a solution of the above-mentioned oily substance in tetrahydrofuran (10 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (10 ml) was slowly added to decompose excess lithium aluminum
20 hydride, and brine (4 ml) was further added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol
25 (7.69 g, yield 80%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (1:2, volume ratio).

¹H-NMR (CDCl₃)δ: 0.83 (6H, t, J= 7.3Hz), 1.35 (1H, t, J= 5.4Hz), 1.60-1.85 (6H, m), 2.40-2.65 (3H, m), 3.67 (2H, q, J= 5.9Hz), 5.24 (2H, s), 7.03-7.40 (6H, m).

Reference Example 236

30 To a mixture of 3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (7.53 g), N-ethyldiisopropylamine (11.5 ml) and tetrahydrofuran (100 ml) was added chloromethyl methyl ether (6.40 ml) at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into
35 water, and extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (0.8 g) and tetrahydrofuran (50 ml) was stirred overnight at 50°C under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with acetone-hexane (2:3, volume ratio). 3-(1-Ethylpropyl)-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (4.93 g, yield 77%) was obtained as a colorless oil.

1H -NMR ($CDCl_3$) δ : 0.82 (6H, d, $J=7.3$ Hz), 1.50-1.94 (6H, m), 2.44-2.70 (3H, m), 3.38 (3H, s), 3.57 (2H, t, $J=6.4$ Hz), 4.64 (2H, s), 7.36 (1H, s).

Reference Example 237

A mixture of 3-ethylsalicylaldehyde (8.10 g), benzyl bromide (11.07 g), potassium carbonate (8.94 g) and N,N-dimethylformamide (30 ml) was stirred at 50°C for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-ethylbenzaldehyde (12.50 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:98, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.27 (3H, t, $J=7.6$ Hz), 2.76 (2H, q, $J=7.6$ Hz), 4.98 (2H, s), 7.22 (1H, t, $J=7.6$ Hz), 7.39-7.43 (5H, m), 7.51-7.53 (1H, m), 7.70-7.72 (1H, m), 10.28 (1H, m).

Reference Example 238

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (7.01 g), sodium hydride (60%, in oil, 1.59 g) and N,N-dimethylformamide (165 ml) was stirred at room temperature for

30 minutes. 2-Chloro-4-(trifluoromethyl)pyridine (6.00 g) was added and the mixture was stirred overnight. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was 5 washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1*H*-pyrazol-4-yl}propanoate (9.05 g, yield 77%) was obtained as a pale-yellow oily 10 substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (3H, t, $J = 7.0$ Hz), 1.44 (3H, t, $J = 7.0$ Hz), 2.56 – 2.66 (2H, m), 2.70 – 2.81 (2H, m), 4.15 (2H, q, $J = 7.0$ Hz), 4.37 (2H, q, $J = 7.0$ Hz), 7.18 – 7.24 (1H, m), 7.91 15 – 7.94 (1H, m), 8.18 (1H, s), 8.45 (1H, d, $J = 5.0$ Hz).

Reference Example 239

To a solution of ethyl 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1*H*-pyrazol-4-yl}propanoate (10.2 g) in tetrahydrofuran (280 ml) was dropwise added a 0.93 20 M solution (92.0 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. 1N Hydrochloric acid was added to the reaction mixture and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried 25 (MgSO_4) and concentrated to give 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1*H*-pyrazol-4-yl}-1-propanol (9.07 g, quantitative) as a white solid. The crystals were recrystallized from ethyl acetate-hexane to give colorless 30 crystals. melting point: 73–74°C.

Reference Example 240

A mixture of ethyl 3-isopropyl-1*H*-pyrazole-4-carboxylate (12.8 g), sodium hydride (60%, in oil, 3.08 g) and N,N-dimethylformamide (350 ml) was stirred at room temperature for 30 minutes. 2,5-Dichloropyridine (11.4 g) was added and the 35 mixture was stirred overnight at 100°C. Saturated aqueous

ammonium chloride solution was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). To a solution of the obtained solid in tetrahydrofuran (230 ml) was dropwise added a 1.0 M solution (176 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. Dilute hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and [1-(5-chloro-2-pyridinyl)-3-isopropyl-1*H*-pyrazol-4-yl]methanol (12.6 g, yield 71%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 135-136°C.

Reference Example 241

A mixture of ethyl (E)-3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1*H*-pyrazol-4-yl]propenoate (1.35 g), platinum oxide (100 mg) and ethanol (100 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Platinum oxide was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1*H*-pyrazol-4-yl]propanoate (1.09 g, yield 68%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 70-71°C.

Reference Example 242

To a solution of ethyl 3-[1-(5-chloro-2-pyridinyl)-3-

isopropyl-1*H*-pyrazol-4-yl]propanoate (1.08 g) in tetrahydrofuran (30 ml) was dropwise added a 0.93 M a solution (9.8 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. 1N
5 Hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated to give 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1*H*-pyrazol-4-yl]-1-propanol (0.92 g, quantitative)
10 as a white solid. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 93-95°C.

Reference Example 243

Diethyl ethoxymethylenemalonate (56.9 ml) was added to a
15 solution of ethylhydrazine oxalate (42.6 g) in toluene (150 ml)-acetic acid (150 ml)-water (100 ml) and the mixture was stirred at room temperature for 1 hour, and at 100°C overnight. The reaction solution was cooled to room temperature, the organic solvent was evaporated under reduced pressure, and the
20 residue was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was washed with diisopropyl ether to give a pale-yellow solid. A mixture of the obtained solid, benzyl bromide (29.0 ml),
25 potassium carbonate (33.7 g) and N,N-dimethylformamide (350 ml) was stirred at room temperature for 2.5 days and saturated aqueous ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
30 chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-benzyloxy-1-ethyl-1*H*-pyrazole-4-carboxylate (34.0 g, yield 43%) was obtained as a pale yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
35 $^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (3H, t, $J = 7.4$ Hz), 1.46 (3H, t, $J = 7.4$

Hz), 4.01 (2H, q, J = 7.4 Hz), 4.27 (2H, q, J = 7.4 Hz), 5.34 (2H, s), 7.22 – 7.42 (3H, m), 7.46 – 7.54 (2H, m), 7.72 (1H, s).

Reference Example 244

To a mixture of ethyl 3-benzyloxy-1-ethyl-1*H*-pyrazole-4-carboxylate (34.0 g) and tetrahydrofuran (500 ml) was slowly added lithium aluminum hydride (4.70 g) at 0°C and the mixture was stirred at room temperature for 1.5 hours. 1N Hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)methanol (19.9 g, yield 69%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:2, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (3H, t, J = 7.2 Hz), 3.98 (2H, d, J = 7.2 Hz), 4.47 (2H, s), 5.24 (2H, s), 7.20 (1H, s), 7.27 – 7.39 (3H, m), 7.40 – 7.46 (2H, m).

Reference Example 245

To a mixture of (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)methanol (1.40 g), acetone cyanohydrin (1.10 ml), tributylphosphine (3.00 ml) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (3.04 g) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetonitrile (0.72 g, yield 49%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (3H, t, J = 7.2 Hz), 3.43 (2H, s), 3.99 (2H, q, J = 7.2 Hz), 5.22 (2H, s), 7.23 – 7.46 (6H, m).

Reference Example 246

A mixture of (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetonitrile (720 mg), 6N aqueous sodium hydroxide solution

(20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred under reflux for 2 days. After cooling, the reaction mixture was acidified by adding 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was 5 washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. A mixture of the residue, a 10% solution (30 ml) of hydrochloric acid in methanol and methanol (30 ml) was stirred at room temperature for 2.5 hours. After concentration, the residue was subjected to silica gel column 10 chromatography, and methyl (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetate (470 mg, yield 57%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (3H, t, $J = 7.2$ Hz), 3.40 (2H, s), 3.68 15 (3H, s), 3.98 (2H, q, $J = 7.2$ Hz), 5.22 (2H, s), 7.23 (1H, s), 7.27 – 7.39 (3H, m), 7.40 – 7.47 (2H, m).

Reference Example 247

A mixture of methyl (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetate (11.0 g), 5% palladium-carbon (2.19 g) and ethanol 20 (300 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (1-ethyl-3-hydroxy-1*H*-pyrazol-4-yl)acetate (7.17 g, yield 97%) 25 was obtained as a white solid from a fraction eluted with ethyl acetate. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 72–73°C.

Reference Example 248

To a solution of cyclohexylhydrazine hydrochloride (30.0 g) in toluene (100 ml)-acetic acid (100 ml) was added sodium acetate (16.3 g) and the mixture was reacted at room temperature for 10 minutes. A solution of diethyl ethoxymethylenemalononate (39.8 ml) was added and the mixture 35 was stirred overnight at 80°C. After cooling the reaction

solution to room temperature, the resulting precipitate was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 1-cyclohexyl-3-hydroxy-1*H*-pyrazole-4-carboxylate (46.2 g, yield 97%) was obtained as a purple solid from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 91-92°C.

Reference Example 249

A mixture of ethyl 1-cyclohexyl-3-hydroxy-1*H*-pyrazole-4-carboxylate (46.0 g), benzyl bromide (24.1 ml), potassium carbonate (28.1 g) and N,N-dimethylformamide (400 ml) was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-benzyloxy-1-cyclohexyl-1*H*-pyrazole-4-carboxylate (61.5 g, yield 97%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10 - 1.28 (3H, m), 1.37 (3H, t, J = 7.2 Hz), 1.38 - 1.49 (2H, m), 1.56 - 1.82 (5H, m), 3.81 - 3.92 (1H, m), 4.31 (2H, q, J = 7.2 Hz), 5.41 (2H, s), 7.32 - 7.39 (5H, m), 7.77 (1H, s).

Reference Example 250

To a mixture of ethyl 3-benzyloxy-1-cyclohexyl-1*H*-pyrazole-4-carboxylate (31.5 g) and tetrahydrofuran (300 ml) was slowly added lithium aluminum hydride (2.73 g) at 0°C and the mixture was stirred at room temperature for 1.5 hours. Aluminum lithium hydride (1.81 g) was added, and the mixture was stirred at room temperature for 1 hour. 1N Hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N

hydrochloric acid and saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)methanol (16.5 g, yield 5 60%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.14 – 1.35 (3H, m), 1.40 – 1.86 (1H, brm), 1.59 – 1.86 (7H, m), 3.87 – 4.00 (1H, m), 4.48 (2H, d, J = 4.5 Hz), 5.24 (2H, s), 7.31 – 7.41 (6H, m).

10 **Reference Example 251**

To a mixture of (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)methanol (16.5 g), acetone cyanohydrin (8.77 ml), tributylphosphine (21.5 ml) and tetrahydrofuran (350 ml) was added a 40% solution (39.1 ml) of diethyl azodicarboxylate in 15 toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and diisopropyl ether was added to the residue. The resulting unnecessary material was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel 20 column chromatography, and a pale yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 6N aqueous sodium hydroxide solution (100 ml), tetrahydrofuran (100 ml) and ethanol (100 ml) was stirred under reflux for one 25 day. After cooling to room temperature, the reaction solution was concentrated. The residue was diluted with water (300 ml) and washed with ethyl acetate. The aqueous layer was acidified by adding conc. hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated 30 aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated to give (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetic acid (7.86 g, yield 44%) as a yellow oily substance.

1H -NMR ($CDCl_3$) δ : 1.14 – 1.28 (3H, m), 1.54 – 1.84 (7H, m), 3.40 (2H, s), 3.76 – 3.92 (1H, m), 5.05 (2H, s), 7.32 – 7.41 (6H, 35 m).

Reference Example 252

A mixture of (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetic acid (7.86 g), a 10% solution (125 ml) of hydrochloric acid in methanol and methanol (125 ml) was stirred overnight at room temperature. The reaction solution was concentrated and the residue was diluted with ethyl acetate. The diluted solution was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetate (1.98 g, yield 24%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.12 – 1.30 (3H, m), 1.52 – 1.84 (7H, m), 3.38 (2H, s), 3.70 (3H, s), 3.76 – 3.89 (1H, m), 5.06 (2H, s), 7.33 – 7.42 (6H, m).

Reference Example 253

A mixture of methyl (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetate (1.98 g), 5% palladium-carbon (400 mg) and ethanol (60 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (1-cyclohexyl-3-hydroxy-1*H*-pyrazol-4-yl)acetate (1.24 g, yield 92%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 135–136°C.

Reference Example 254

To a solution of diethyl 2-formylsuccinate (2.02 g) in ethanol (15 ml) was dropwise added a solution of methylhydrazine (580 μl) in ethanol (5 ml) at 0°C. The reaction solution was stirred at 0°C for 30 minutes and at room temperature for 1 hour, followed by heating to 80°C. After stirring at said temperature overnight, the reaction solution

was concentrated. The obtained brown solid was recrystallized from ethyl acetate-hexane to give ethyl (5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)acetate (1.42 g, yield 77%) as colorless crystals. melting point: 104–105°C.

5 Reference Example 255

To a solution of ethylhydrazine oxalate (4.08 g) in ethanol (30 ml) was added sodium ethoxide (3.70 g) at 0°C. The mixture was stirred at room temperature for 1 hour and a solution of diethyl 2-formylsuccinate (5.00 g) in ethanol (30 ml) was dropwise added at 0°C. The reaction solution was stirred at 0°C for 30 minutes and at room temperature for 2 hours, which was followed by heating until reflux. After stirring at said temperature overnight, the reaction solution was cooled to room temperature, and the resulting precipitate was removed by filtration. The filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and ethyl (1-ethyl-5-hydroxy-1*H*-pyrazol-4-yl)acetate (2.36 g, yield 48%) was obtained as a brown solid from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 107–108°C.

Reference Example 256

To a solution of ethyl hydrazinoacetate hydrochloride (3.56 g) in ethanol (25 ml) was added 1N aqueous sodium hydroxide solution (23.1 ml) at 0°C. The reaction solution was stirred at room temperature for 1 hour and a solution of ethyl 2-formylpropanoate (3.00 g) in ethanol (75 ml) was dropwise added at 0°C. The reaction solution was stirred at room temperature for 1 hour, which was followed by heating until reflux. After stirring overnight, the reaction solution was cooled to room temperature, and concentrated. The obtained residue was subjected to silica gel column chromatography, and ethyl (5-hydroxy-4-methyl-1*H*-pyrazol-1-yl)acetate (3.35 g, yield 79%) was obtained as a colorless oil from a fraction eluted with methanol-ethyl acetate (1:7, volume ratio).

¹H-NMR (CDCl₃)δ: 1.25 – 1.32 (3H, m), 1.39 (1.0H, d, J = 8.1 Hz), 1.89 (2H, s), 3.22 (0.3H, t, J = 8.1 Hz), 4.17 – 4.26 (2H, m), 4.45 (0.6H, s), 4.58 (1.4H, s), 7.22 – 7.24 (0.7H, m), 7.29 – 7.31 (0.3H, m).

5 **Reference Example 257**

To a solution of ethyl hydrazinoacetate hydrochloride (1.64 g) in ethanol (10 ml) was dropwise added 1N aqueous sodium hydroxide solution (10.6 ml) at 0°C. The reaction solution was stirred at room temperature for 1 hour and a 10 solution of ethyl 2-formylbutanoate (2.13 g) in ethanol (30 ml) was dropwise added at 0°C. The reaction solution was stirred at room temperature for 2.5 hours, and at 80°C overnight. The reaction solution was cooled to room temperature and concentrated. The obtained residue was 15 subjected to silica gel column chromatography, and ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (1.54 g, yield 81%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (19:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless 20 crystals. melting point: 77–78°C.

Reference Example 258

A mixture of ethyl (E)-3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]propenoate (30.25 g), 5% palladium-carbon (3.5 g) and tetrahydrofuran (200 ml) was stirred overnight at room 25 temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (11.73 g, yield 39%) was obtained as a yellow oily substance 30 from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

¹H-NMR (CDCl₃)δ: 1.20 (3H, t, J= 7.2Hz), 1.30 (6H, d, J= 7.0Hz), 2.44–2.55 (2H, m), 2.68–2.79 (2H, m), 2.99 (1H, septet, J= 7.0Hz), 4.09 (2H, q, J= 7.2Hz), 5.23 (2H, s), 7.12– 35 7.40 (6H, m).

Reference Example 259

Ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (10.06 g, yield 47%) was obtained as a yellow oily substance from a fraction eluted following the compound described in
5 Reference Example 258 in the silica gel column chromatography described in Reference Example 258.

¹H-NMR (CDCl₃)δ: 1.25 (3H, t, J= 7.2Hz), 1.29 (6H, d, J= 7.0Hz), 2.50-2.60 (2H, m), 2.72-2.83 (2H, m), 3.06 (1H, septet, J= 7.0Hz), 4.14 (2H, q, J= 7.2Hz), 7.34 (1H, s).

10 Reference Example 260

To a mixture of 2-benzyloxy-3-ethylbenzaldehyde (12.40 g), methyl (methylthio)methyl sulfoxide (12.82 g) and tetrahydrofuran (100 ml) was added a 40% solution (2.00 ml) of benzyltrimethylammonium hydroxide in methanol at room
15 temperature, and the mixture was stirred at 65°C for 2 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 2-(2-benzyloxy-3-ethylphenyl)-1-(methylthio)vinyl methyl sulfoxide (15.20 g, yield 85%) was obtained as a yellow oily substance
20 from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

¹H-NMR (CDCl₃)δ: 1.24 (3H, t, J=7.6 Hz), 2.29 (3H, s), 2.72 (2H, q, J=7.6 Hz), 2.72 (3H, s), 4.79-4.82 (2H, m), 7.16 (1H, t, J=7.6 Hz), 7.29 (1H, dd, J=7.6,1.6Hz), 7.32-7.42 (3H, m),
25 7.49-7.51 (2H, m), 7.95 (1H, dd, J=7.6,1.6Hz), 8.03 (1H, s).

Reference Example 261

A mixture of 2-(2-benzyloxy-3-ethylphenyl)-1-(methylthio)vinyl methyl sulfoxide (14.90 g), a 10% solution (100 ml) of hydrogen chloride in methanol and methanol (100 ml) was refluxed for 16 hours. The reaction solution was concentrated. Ethyl acetate and aqueous sodium hydrogen carbonate were added to the residue and the mixture extracted. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and
30 35

methyl (2-benzyloxy-3-ethylphenyl)acetate (9.60 g, yield 79%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (4:96, volume ratio).

¹H-NMR (CDCl₃) δ : 1.25 (3H, t, J=7.6 Hz), 2.73 (2H, q, J=7.6 Hz), 3.66 (3H, s), 3.69 (2H, s), 4.84 (2H, s), 7.08 (1H, t, J=7.6 Hz), 7.13 (1H, dd, J=7.6,1.6Hz), 7.19 (1H, dd, J=7.6,1.6Hz), 7.32-7.43 (3H, m), 7.46-7.48 (2H, m).

Reference Example 262

A mixture of methyl (2-benzyloxy-3-ethylphenyl)acetate (9.20 g), 5% palladium-carbon (1.00 g) and methanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-ethyl-2-hydroxyphenyl)acetate (5.40 g, yield 86%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ : 1.23 (3H, t, J=7.6 Hz), 2.69 (2H, q, J=7.6 Hz), 3.68 (2H, s), 3.75 (3H, s), 6.83 (1H, t, J=7.6 Hz), 6.94 (1H, dd, J=7.6,1.6Hz), 7.10 (1H, dd, J=7.6,1.2Hz), 7.53 (1H, s).

Reference Example 263

A mixture of 2-coumaranone (25.00 g), a 10% solution (30 ml) of hydrogen chloride in methanol and methanol (30 ml) was stirred at 50°C for 30 minutes. The reaction solution was concentrated. Ethyl acetate and aqueous sodium hydrogen carbonate were added to the residue and the mixture was extracted. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-hydroxyphenyl)acetate (30.60 g, yield 99%) was obtained as a colorless oil from a fraction eluted with diethyl ether.

¹H-NMR (CDCl₃) δ : 3.68 (2H, s), 3.74 (3H, s), 6.86-6.93 (2H, m), 7.10 (1H, dd, J=7.2,1.6 Hz), 7.16-7.20 (1H, m), 7.35 (1H,

brs).

Reference Example 264

To a mixture of methyl (2-hydroxyphenyl)acetate (4.99 g), diisopropylamine (610 mg) and methylene chloride (300 ml) was slowly added N-bromosuccinimide (5.34 g) under ice-cooling, and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-bromo-2-hydroxyphenyl)acetate (5.60 g, yield 76%) was obtained as a colorless oil from a fraction eluted with chloroform.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.71 (2H, s), 3.73 (3H, s), 6.32 (1H, s), 6.78 (1H, t, $J=8.0$ Hz), 7.11 (1H, dt, $J=8.0, 0.8$ Hz), 7.41 (1H, dd, $J=8.0, 1.6$ Hz).

Reference Example 265

A mixture of methyl (3-bromo-2-hydroxyphenyl)acetate (4.30 g), benzyl bromide (3.30 g), potassium carbonate (4.84 g) and acetone (50 ml) was refluxed for 1 hour. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-bromophenyl)acetate (4.10 g, yield 70%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (4:96, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.65 (3H, s), 3.66 (2H, s), 5.01 (2H, s), 7.00 (1H, t, $J=8.0$ Hz), 7.23 (1H, dd, $J=8.0, 1.2$ Hz), 7.33-7.43 (3H, m), 7.49-7.54 (3H, m).

Reference Example 266

A mixture of methyl (2-benzyloxy-3-bromophenyl)acetate (2.01 g), copper(I) cyanide (2.14 g) and N,N -dimethylformamide (30 ml) was stirred at 190°C for 16 hours. The reaction mixture was poured into a mixture of iron(III) chloride and dilute hydrochloric acid. The mixture was stirred for 1 hour and extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-cyanophenyl)acetate (1.20 g, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

1H -NMR ($CDCl_3$) δ : 3.62 (2H, s), 3.64 (3H, s), 5.24 (2H, s), 7.16 (1H, t, $J=7.6$ Hz), 7.34-7.42 (3H, m), 7.46-7.50 (3H, m), 7.57 (1H, dd, $J=7.6,1.6$ Hz).

10 **Reference Example 267**

A mixture of methyl (2-benzyloxy-3-cyanophenyl)acetate (1.10 g), 5% palladium-carbon (110 mg) and methanol (15 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-cyano-2-hydroxyphenyl)acetate (700 mg, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

20 1H -NMR ($CDCl_3$) δ : 3.73 (2H, s), 3.80 (3H, s), 6.95 (1H, t, $J=7.6$ Hz), 7.31 (1H, dt, $J=7.6,0.8$ Hz), 7.48 (1H, dd, $J=7.6,1.6$ Hz).

Reference Example 268

A mixture of methyl (2-benzyloxy-3-bromophenyl)acetate (1.90 g), copper(I) chloride (2.24 g) and N,N-dimethylformamide (20 ml) was stirred at 190°C for 16 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-chlorophenyl)acetate (740 mg, yield 45%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:98, volume ratio).

35 1H -NMR ($CDCl_3$) δ : 3.64 (2H, s), 3.65 (3H, s), 5.02 (2H, s), 7.05 (1H, t, $J=8.0$ Hz), 7.17 (1H, dd, $J=8.0,1.6$ Hz), 7.34-7.42 (4H,

m), 7.46-7.51 (2H, m).

Reference Example 269

A mixture of methyl (2-benzyloxy-3-chlorophenyl)acetate (680 mg), 5% palladium-carbon (70 mg) and methanol (15 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-chloro-2-hydroxyphenyl)acetate (300 mg, yield 64%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃)δ: 3.70 (2H, s), 3.73 (3H, s), 6.28 (1H, s), 6.84 (1H, t, J=8.0 Hz), 7.08 (1H, dd, J=8.0,0.8 Hz), 7.27 (1H, dd, J=8.0,1.0 Hz).

15 Reference Example 270

To a mixture of ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (1.50 g), 2-chloro-5-(trifluoromethyl)-1,3,4-thiadiazole (1.50 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.34 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl)propanoate (1.29 g, yield 50%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

³⁰ ¹H-NMR (CDCl₃)δ: 1.27 (3H, t, J= 7.1Hz), 1.30 (6H, d, J= 7.0Hz), 2.57-2.90 (4H, m), 3.01 (1H, septet, J= 7.0Hz), 4.17 (2H, q, J= 7.1Hz), 8.13 (1H, s).

Reference Example 271

To a solution of ethyl 3-(3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-

yl)propanoate (1.29 g) in tetrahydrofuran (15 ml) was dropwise added a 1.5M solution (5.7 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate.

The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl)-1-propanol (0.82 g, yield 73%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 89-90°C.

¹⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (6H, d, $J = 7.0\text{Hz}$), 1.45 (1H, br s), 1.82-1.98 (2H, m), 2.62 (2H, t, $J = 7.8\text{Hz}$), 3.00 (1H, septet, $J = 7.0\text{Hz}$), 3.76 (2H, t, $J = 6.0\text{Hz}$), 8.13 (1H, s).

Reference Example 272

To a mixture of 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-1H-pyrazol-3-ol (21.8 g) and N,N-dimethylformamide (150 ml) potassium carbonate (16.7 g) was added diethylsulfuric acid (17.3 ml) at room temperature, and the mixture was stirred overnight. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained residue was subjected to silica gel column chromatography, and 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-3-ethoxy-1H-pyrazole (19.5 g, yield 82%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

$^1\text{H NMR}$ (CDCl_3) δ : 1.36 (3H, t, $J = 6.9\text{ Hz}$), 1.57 - 1.74 (4H, m), 2.32 - 2.39 (2H, m), 3.80 - 3.98 (4H, m), 4.22 (2H, q, $J = 6.9\text{ Hz}$), 4.82 - 4.87 (1H, m), 5.07 (2H, s), 6.93 (1H, s), 7.13 - 7.17 (2H, m), 7.23 - 7.35 (3H, m).

Reference Example 273

A mixture of 3,3-dimethyl-2-butanone (6.19 ml) and bis(dimethylamino)methoxymethane (6.61 g) was heated under reflux for 10 hours. The reaction mixture was concentrated under reduced pressure. Hydrazine monohydrate (1.60 g) and n-butyl alcohol (24.9 ml) were added to the residue, and the mixture was heated under reflux for 7 hours. The reaction mixture was concentrated under reduced pressure to give 3-tert-butyl-1H-pyrazole (3.79 g, yield 61%) as a yellow oily substance.

¹H-NMR (CDCl₃) δ: 1.34 (9H, s), 6.10 (1H, d, J=2.0 Hz), 7.49 (1H, d, J=2.0 Hz), 10.3 (1H, br s).

Reference Example 274

To a mixture of 3-tert-butyl-1H-pyrazole (3.72 g), 2-chloro-5-(trifluoromethyl)pyridine (5.45 g) and N-methylpyrrolidone (18.6 ml) was added sodium hydroxide (1.80 g) while stirring the mixture at room temperature. After allowing reaction as it was for 8 hours, water (38 ml) and 6N hydrochloric acid (80 ml) were added and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and eluted with hexane and then with toluene to give 2-(3-tert-butyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (7.04 g, yield 87%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.37 (9H, s), 6.37 (1H, d, J=2.6 Hz), 7.97 (1H, dd, J=8.7, 2.1 Hz), 8.08 (1H, d, J=8.7 Hz), 8.46 (1H, d, J=2.7 Hz), 8.6-8.7 (1H, m).

Reference Example 275

Iodine (3.91 g) and successively diammonium cerium(IV) nitrate (844 mg) were added to a solution of 2-(3-tert-butyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (6.93 g) in acetonitrile (139 ml) while stirring the mixture at room temperature, and the reaction was continued for 5 hours. After the completion of the reaction, the reaction mixture was

concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous sodium thiosulfate solution, dried (magnesium sulfate) and concentrated under reduced pressure to give 2-(3-tert-butyl-4-⁵ iodo-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (9.82 g, yield 96%) as a yellow oily substance.

¹H-NMR (CDCl₃) δ: 1.49 (9H, s), 7.97 (1H, dd, J=8.7, 2.1 Hz), 8.03 (1H, d, J=8.7 Hz), 8.59 (1H, s), 8.6-8.7 (1H, m).

¹⁰ **Reference Example 276**

A mixture of 2-(3-tert-butyl-4-iodo-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (8.68 g), palladium acetate (494 mg), triphenylphosphine (1.15 g), sodium acetate (3.61 g), benzyltriethylammonium chloride (5.01 g), methyl acrylate (7.89 ml) and N-methylpyrrolidone (86.8 ml) was stirred in a nitrogen stream at an outer temperature of 80°C for 17 hours. The reaction mixture was cooled to room temperature and an insoluble material was removed by filtration. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with water, dried (sodium sulfate) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and methyl (E)-3-(3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-2-propenoate (¹⁵ 5.43 g, yield 70%) was obtained as a white solid and was obtained from a fraction eluted with hexane-ethyl acetate (19:1, volume ratio).

¹H-NMR (CDCl₃) δ: 1.44 (9H, s), 3.80 (3H, s), 6.26 (1H, d, J=15.8 Hz), 7.86 (1H, d, J=15.8 Hz), 8.00 (1H, dd, J=8.6, 2.2 Hz), 8.10 (1H, d, J=8.7 Hz), 8.65 (1H, d, J=2.2 Hz), 8.77 (1H, s).

Reference Example 277

To a mixture of methyl (E)-3-(3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-2-propenoate (²⁰ 3.00 g), 5% palladium-carbon (9.00 g), ethanol (50 ml) and

tetrahydrofuran (10 ml) was added formic acid (25 ml), and the mixture was stirred for 2 hours with heating under reflux. The reaction mixture was cooled to room temperature and palladium-carbon was removed by filtration. The filtrate was
5 concentrated under reduced pressure and the residue was diluted with ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried ($MgSO_4$) and concentrated to give a white solid. To a solution of the obtained solid in
10 tetrahydrofuran (100 ml) was dropwise added a 0.93M solution (26.9 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature for 30 minutes. 1N Hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was
15 washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (2.74 g, yield 98%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane
20 (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 69-70°C.

Reference Example 278

A mixture of 3-tert-butyl-1H-pyrazole (2.00 g), sodium hydride (60% in oil, 773 mg) and N,N-dimethylformamide (80 ml) was stirred at room temperature for 30 minutes, and benzyl bromide (2.11 ml) was added. The mixture was stirred overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
25 washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-3-tert-butyl-1H-pyrazole (3.44 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

35 1H -NMR ($CDCl_3$) δ : 1.33 (9H, s), 5.27 (2H, s), 6.10 (1H, d,

$J=2.4$ Hz), 7.14–7.19 (3H, m), 7.24–7.37 (3H, m).

Reference Example 279

A mixture of 1-benzyl-3-tert-butyl-1H-pyrazole (3.44 g), iodine (2.44 g), diammonium cerium(IV) nitrate (5.28 g) and 5 acetonitrile (80 ml) was stirred overnight at room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrosulfite solution and saturated brine, dried ($MgSO_4$) and concentrated to 10 give 1-benzyl-3-tert-butyl-4-iodo-1H-pyrazole (5.34 g, yield 97%) as a green oily substance.

1H -NMR ($CDCl_3$) δ : 1.44 (9H, s), 5.21 (2H, s), 7.18–7.26 (3H, m), 7.27–7.38 (3H, m).

Reference Example 280

To a mixture of 1-benzyl-3-tert-butyl-4-iodo-1H-pyrazole (5.34 g), palladium(II) acetate (353 mg), triphenylphosphine (824 mg), benzyltriethylammonium chloride (3.58 g), methyl acrylate (5.63 ml) and 1-methyl-2-pyrrolidone (62.8 ml) was 15 added sodium acetate (2.58 g) at room temperature, and the mixture was heated to 80°C under an argon atmosphere. The mixture was stirred overnight at said temperature. The reaction mixture was cooled to room temperature, and an insoluble material was removed by filtration. Water was added to the filtrate, and the mixture was extracted with ethyl 20 acetate. The extract was washed with water and saturated aqueous sodium hydrosulfite solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (E)-3-(1-benzyl-3-tert-butyl-1H-pyrazol-4-yl)-2-propenoate (3.24 g, yield 69%) was obtained as 25 a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.40 (9H, s), 3.75 (3H, s), 5.23 (2H, s), 5.93 (1H, d, $J=15.8$ Hz), 7.20–7.28 (2H, m), 7.31–7.40 (3H, m), 7.47 (1H, s), 7.84 (1H, d, $J=15.8$ Hz).

Reference Example 281

To a mixture of methyl (E)-3-(1-benzyl-3-tert-butyl-1H-pyrazol-4-yl)-2-propenoate (3.24 g), 5% palladium-carbon (9.00 g), ethanol (50 ml) and tetrahydrofuran (10 ml) was added 5 formic acid (25 ml), and the mixture was stirred overnight while heating under reflux. The reaction mixture was cooled to room temperature and palladium-carbon was removed by filtration. The filtrate was concentrated and the residue was diluted with ethyl acetate. The obtained ethyl acetate 10 solution was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried (MgSO_4) and concentrated to give methyl 3-(3-tert-butyl-1H-pyrazol-4-yl)propanoate (2.08 g, yield 91%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (9H, s), 2.57-2.65 (2H, m), 2.88-2.95 (2H, m), 3.69 (3H, s), 7.33 (1H, s).

Reference Example 282

To a mixture of 3-hydroxy-2-methylisonicotinic acid (4.52 g), potassium carbonate (18.6 g) and N,N-dimethylformamide (200 ml) was added benzyl bromide (15.9 ml) at room 20 temperature and the mixture was stirred for 3.5 days. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried (MgSO_4) and concentrated. The residue 25 was subjected to silica gel column chromatography, and benzyl 3-(benzyloxy)-2-methylisonicotinate (4.18 g, yield 43%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.55 (3H, s), 4.94 (2H, s), 5.34 (2H, s), 30 7.30-7.44 (10H, m), 7.48 (1H, d, $J=5.1$ Hz), 8.35 (1H, d, $J=5.1$ Hz).

Reference Example 283

To a solution of benzyl 3-(benzyloxy)-2-methylisonicotinate (4.18 g) in tetrahydrofuran (100 ml) was 35 dropwise added a 0.93M solution (45.0 ml) of

diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at said temperature for 1 hour. Sodium sulfate 10 hydrate (13.5 g) was added to the reaction mixture and the mixture was stirred overnight at room temperature. The resulting insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [3-(benzyloxy)-2-methyl-4-pyridinyl]methanol (2.50 g, yield 87%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (4:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 130-131°C.

Reference Example 284

To a mixture of [3-(benzyloxy)-2-methyl-4-pyridinyl]methanol (2.40 g), acetone cyanohydrin (2.14 ml), tributylphosphine (5.23 ml) and tetrahydrofuran (200 ml) was added 1,1'-azodicarbonyldipiperidine (5.30 g) at room temperature and the mixture was stirred for 1 hour. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a orange oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, potassium hydroxide (2.95 g), water (25 ml) and ethanol (100 ml) was stirred overnight while heating under reflux. The reaction mixture was concentrated, and the residue was diluted with water. The obtained aqueous solution was washed with ether, carefully neutralized with conc. hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$) and concentrated to give [3-(benzyloxy)-2-methyl-4-pyridinyl]acetic acid (1.41 g, yield 52%) as a brown solid. 1H -NMR ($CDCl_3$) δ : 2.54 (3H, s), 3.69 (2H, s), 4.90 (2H, s), 7.20 (1H, d, $J=5.1$ Hz), 7.30-7.48 (5H, m), 8.25 (1H, d, $J=5.1$ Hz).

Reference Example 285

To a mixture of [3-(benzyloxy)-2-methyl-4-pyridinyl]acetic acid (1.41 g), potassium carbonate (2.28 g) and N,N-dimethylformamide (50 ml) was added methyl iodide (1.02 ml) at room temperature and the mixture was stirred for 2 hours. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl [3-(benzyloxy)-2-methyl-4-pyridinyl]acetate (1.46 g, yield 98%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.57 (3H, s), 3.63 (2H, s), 3.67 (3H, s), 4.87 (2H, s), 7.07 (1H, d, $J=5.2$ Hz), 7.30 – 7.50 (5H, m), 8.25 (1H, d, $J=5.2$ Hz).

Reference Example 286

A mixture of methyl [3-(benzyloxy)-2-methyl-4-pyridinyl]acetate (1.46 g), 5% palladium-carbon (500 mg) and ethanol (60 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-hydroxy-2-methyl-4-pyridinyl)acetate (671 mg, yield 69%) was obtained as a yellow oily substance from a fraction eluted with methanol-ethyl acetate (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.51 (3H, s), 3.70 (2H, s), 3.78 (3H, s), 6.89 (1H, d, $J=5.0$ Hz), 8.01 (1H, d, $J=5.0$ Hz).

Reference Example 287

To a mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (3.34 g), acetone cyanohydrin (2.20 g), tributylphosphine (4.76 g) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (5.90 g) at room temperature and the mixture was stirred for 2 hours. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}acetonitrile (3.30 g, yield 96%) was obtained as a yellow oily substance from a fraction eluted
5 with ethyl acetate-hexane (2:3, volume ratio).

¹H-NMR (CDCl₃) δ: 1.36 (6H, d, J=7.0 Hz), 3.04 (1H, septet, J=6.9 Hz), 3.61 (2H, s), 7.95-8.10 (2H, m), 8.56 (1H, s), 8.62-8.65 (1H, m).

Reference Example 288

10 A mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}acetonitrile (3.30 g), 6N aqueous sodium hydroxide solution (11 ml), ethanol (20 ml) and tetrahydrofuran (20 ml) was refluxed overnight. The reaction mixture was concentrated and water (80 ml) was added. The
15 mixture was washed with diethyl ether. The aqueous layer was acidified by adding conc. hydrochloric acid and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. A mixture of the obtained oily substance, conc. sulfuric acid
20 (0.1 ml) and ethanol (40 ml) was refluxed overnight. The reaction mixture was concentrated and aqueous sodium hydrogen carbonate was added to the residue. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue
25 was subjected to silica gel column chromatography, and ethyl {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}acetate (2.78 g, yield 73%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

30 ¹H-NMR (CDCl₃) δ: 1.28 (3H, t, J=7.1 Hz), 1.32 (6H, d, J=6.9 Hz), 3.02 (1H, septet, J=6.9 Hz), 3.53 (2H, s), 4.18 (2H, q, J=7.1 Hz), 7.91-7.97 (1H, m), 8.04 (1H, d, J=8.4 Hz), 8.46 (1H, s), 8.60-8.62 (1H, m).

Reference Example 289

35 To a mixture of ethyl {3-isopropyl-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}acetate (2.68 g) and tetrahydrofuran (35 ml) was slowly added a 1.5M solution (13.0 ml) of diisobutylaluminum hydride in toluene at 0°C and the mixture was stirred at room temperature for 1 hour. The 5 reaction mixture was poured into dilute hydrochloric acid and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give 2-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-ethanol (1.21 10 g, yield 51%) as colorless crystals. The crystals were recrystallized from ethyl acetate-hexane. melting point: 74-75°C.

1H -NMR ($CDCl_3$) δ : 1.34 (6H, d, $J=7.0$ Hz), 1.58 (1H, t, $J=5.8$ Hz), 2.78 (2H, td, $J=6.6$, 0.8 Hz), 3.05 (1H, septet, $J=6.9$ 15 Hz), 3.87 (2H, q, $J=6.4$ Hz), 7.95 (1H, dd, $J=9.0$, 2.0 Hz), 8.04 (1H, d, $J=8.8$ Hz), 8.36 (1H, s), 8.59-8.61 (1H, m).

Reference Example 290

To a mixture of ethyl 3-[3-(1-ethylpropyl)-1H-pyrazol-4-yl]propanoate (3.34 g), 2,5-dibromopyridine (3.65 g) and N,N-dimethylformamide (20 ml) was added 60% sodium hydride (0.67 g) and the mixture was stirred at 100°C for 4 hours. The 20 reaction mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. Ethanol (20 ml) and conc. sulfuric acid (0.1 ml) were added to the residue and the mixture was stirred at 50°C for 6 hours. The 25 reaction mixture was poured into aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propanoate (3.90 g, yield 71%) was obtained as a white 30 powder from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 0.86 (6H, t, J=7.6 Hz), 1.26 (3H, t, J=7.2 Hz), 1.64-1.80 (4H, m), 2.56-2.64 (3H, m), 2.78-2.81 (2H, m), 4.16 (2H, q, J=7.2 Hz), 7.82-7.83 (2H, m), 8.20 (1H, s), 8.38-8.39 (1H, m).

5 Reference Example 291

To a solution of ethyl 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propanoate (3.80 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (30 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (2.60 g, yield 77%) was obtained as a white powder from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

¹H-NMR (CDCl₃) δ: 0.86 (6H, t, J=7.6 Hz), 1.30 (1H, t, J=5.2Hz), 1.66-1.80 (4H, m), 1.87-1.91 (2H, m), 2.54-2.60 (3H, m), 3.72-3.76 (2H, m), 7.83 (2H, m), 8.20 (1H, s), 8.38-8.39 (1H, m).

Reference Example 292

To a mixture of 2-isopropylphenol (13.62 g), tributylamine (7.41 g) and toluene (50 ml) was added tin tetrachloride (1.18 ml) at room temperature and the mixture was stirred for 30 minutes. Paraformaldehyde (6.60 g) was added, and the mixture was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 2-hydroxy-3-isopropylbenzaldehyde (9.90 g, yield 60%) was obtained as a colorless oil from a fraction eluted with hexane.

¹H-NMR (CDCl₃) δ: 1.25 (6H, t, J=6.8 Hz), 3.30-3.40 (1H, m),

6.99 (1H, t, J=7.6 Hz), 7.40 (1H, dd, J=7.6, 1.6 Hz), 7.47 (1H, dd, J=7.6, 1.6 Hz), 9.89 (1H, s), 11.37 (1H, s).

Reference Example 293

A mixture of 2-hydroxy-3-isopropylbenzaldehyde (8.10 g),
5 benzyl bromide (10.12 g), potassium carbonate (8.18 g) and
N,N-dimethylformamide (30 ml) was stirred at 50°C for 1 hour.
The reaction mixture was poured into dilute hydrochloric acid,
and extracted with ethyl acetate. The ethyl acetate layer was
washed with saturated brine, dried ($MgSO_4$) and concentrated.
10 The residue was subjected to silica gel column chromatography,
and 2-benzyloxy-3-isopropylbenzaldehyde (11.70 g, yield 93%)
was obtained as a colorless oil from a fraction eluted with
ethyl acetate-hexane (2:98, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.25 (6H, d, J=6.8 Hz), 3.40-3.46 (1H, m),
15 4.97 (2H, s), 7.25 (1H, t, J=7.8 Hz), 7.36-7.44 (5H, m), 7.57
(1H, dd, J=7.8, 1.8Hz), 7.71 (1H, dd, J=7.8, 1.8 Hz), 10.30
(1H, s).

Reference Example 294

To a mixture of 2-benzyloxy-3-isopropylbenzaldehyde
20 (11.50 g), methyl (methylthio)methyl sulfoxide (11.23 g) and
tetrahydrofuran (100 ml) was added a 40% solution (2.00 ml) of
benzyltrimethylammonium hydroxide in methanol at room
temperature and the mixture was stirred at 65°C for 2 hours.
The reaction solution was concentrated. The residue was
25 subjected to silica gel column chromatography, and 2-[2-(benzyloxy)-3-isopropylphenyl]-1-(methylthio)vinyl methyl
sulfoxide (13.50 g, yield 83%) was obtained as a yellow oily
substance from a fraction eluted with ethyl acetate-hexane
(1:1, volume ratio).
30 ¹H-NMR ($CDCl_3$) δ : 1.22 (6H, dd, J=6.8, 0.8 Hz), 2.30 (3H, s),
2.72 (3H, s), 3.35-3.43 (1H, m), 4.76-4.82 (2H, m), 7.19 (1H,
t, J=7.8 Hz), 7.32-7.43 (4H, m), 7.49-7.52 (2H, m), 7.93 (1H,
dd, J=7.8, 1.6 Hz), 8.05 (1H, s).

Reference Example 295

35 A mixture of 2-[2-(benzyloxy)-3-isopropylphenyl]-1-

(methylthio)vinyl methyl sulfoxide (13.30 g) and a 10% solution (100 ml) of hydrogen chloride in methanol was refluxed for 2 hours. The reaction solution was concentrated and ethyl acetate and aqueous sodium hydrogen carbonate were added to the residue and the mixture was extracted. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-isopropylphenyl)acetate (8.90 g, yield 80%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (4:96, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J=6.8$ Hz), 3.32-3.44 (1H, m), 3.67 (3H, s), 3.71 (2H, s), 4.84 (2H, s), 7.11-7.14 (2H, m), 7.24 (1H, dd, $J=6.4$, 3.2 Hz), 7.35-7.43 (3H, m), 7.47-7.49 (2H, m).

Reference Example 296

A mixture of methyl (2-benzyloxy-3-isopropylphenyl)acetate (8.40 g), 5% palladium-carbon (0.80 g) and methanol (80 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-hydroxy-3-isopropylphenyl)acetate (4.80 g, yield 82%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J=6.8$ Hz), 3.32-3.43 (1H, m), 3.68 (2H, s), 3.75 (3H, s), 6.83 (1H, t, $J=7.6$ Hz), 6.93 (1H, dd, $J=7.6$, 1.2 Hz), 7.16 (1H, dd, $J=7.6$, 2.0 Hz), 7.66 (1H, s).

30 Reference Example 297

To a mixture of ethyl 3-(3-isopropyl-1*H*-pyrazol-4-yl)propanoate (0.50 g), 2-chloro-3-(trifluoromethyl)pyridine (0.43 g) and *N,N*-dimethylformamide (10 ml) was added 60% sodium hydride (0.1 g) at 100°C and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute

hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. Ethanol (10 ml) and conc. sulfuric acid (0.05 ml) were added to the residue and the mixture was
5 stirred at 70°C for 2 hours. The reaction mixture was poured into an aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography,
10 and ethyl 3-(3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propanonate (0.60 g, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl_3) δ : 1.26 (3H, t, $J=7.2$ Hz), 1.32 (6H, d, $J=7.2$ Hz), 2.62-2.66 (2H, m), 2.82-2.86 (2H, m), 2.99-3.06 (1H, m),
15 4.15 (2H, q, $J=7.2$ Hz), 7.32 (1H, dd, $J=8.0, 4.8$ Hz), 7.96 (1H, s), 8.14 (1H, dd, $J=8.0, 1.6$ Hz), 8.59 (1H, dd, $J=4.8, 1.6$ Hz).

Reference Example 298

20 To a solution of ethyl 3-(3-isopropyl -1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propanoate (0.60 g) in tetrahydrofuran (10 ml) was dropwise added a 1.0 M solution (10 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature for 2 hours.
25 The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (0.44 g, yield 83%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).
30

¹H-NMR (CDCl_3) δ : 1.32 (6H, d, $J=6.8$ Hz), 1.88-1.95 (2H, m), 2.58-2.62 (2H, m), 2.98-3.05 (1H, m), 3.73-3.76 (2H, m), 7.29-
35 7.33 (1H, m), 7.96 (1H, s), 8.14 (1H, dd, $J=8.2, 1.2$ Hz), 8.59

(1H, dd, J=4.8, 1.6 Hz).

Reference Example 299

To a mixture of ethyl 3-(3-isopropyl-1H-pyrazol-4-yl)propanoate (0.50 g), 2-chloro-4-(trifluoromethyl)pyridine (0.43 g) and N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.19 g) at 100°C and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. Ethanol (10 ml) and conc. sulfuric acid (0.05 ml) were added to the residue and the mixture was stirred at 70°C for 2 hours. The reaction mixture was poured into an aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (0.54 g, yield 64%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (3H, t, J=7.2 Hz), 1.34 (6H, d, J=7.2 Hz), 2.62-2.66 (2H, m), 2.81-2.85 (2H, m), 3.01-3.08 (1H, m), 4.16 (2H, q, J=7.2 Hz), 7.28 (1H, dd, J=5.2, 1.2 Hz), 8.14 (1H, s), 8.27 (1H, s), 8.50 (1H, d, J=5.2 Hz).

Reference Example 300

To a solution of ethyl 3-(3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propanoate (0.45 g) in tetrahydrofuran (6 ml) was dropwise added a 1.0 M solution (5 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-

pyrazol-4-yl}-1-propanol (0.37 g, yield 93%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

¹H-NMR (CDCl₃) δ: 1.34 (6H, d, J=6.8Hz), 1.89-1.95 (2H, m), 5 2.58-2.62 (2H, m), 3.01-3.08 (1H, m), 3.75 (2H, m), 7.28 (1H, d, J=5.2 Hz), 8.15 (1H, s), 8.26 (1H, s), 8.50 (1H, d, J=5.2 Hz).

Reference Example 301

To a mixture of ethyl 3-(3-isopropyl-1H-pyrazol-4-yl)propanoate (0.63 g), 2-chloro-6-(trifluoromethyl)pyridine (0.55 g) and N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.20 g) at 100°C and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. Ethanol (10 ml) and conc. sulfuric acid (0.05 ml) were added to the residue and the mixture was stirred at 70°C for 2 hours. The reaction mixture was poured into an aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (0.67 g, yield 63%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 1.28 (3H, t, J=7.2 Hz), 1.33 (6H, d, J=7.2 Hz), 2.63-2.67 (2H, m), 2.83 (2H, t, J=8.0 Hz), 3.01-3.07 (1H, m), 4.17 (2H, q, J=7.2 Hz), 7.44 (1H, d, J=7.6 Hz), 7.88-7.92 30 (1H, m), 8.11 (1H, d, J=8.4 Hz), 8.30 (1H, s).

Reference Example 302

To a solution of ethyl 3-(3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propanoate (0.47 g) in tetrahydrofuran (5 ml) was dropwise added a 1.0 M 35 solution (4 ml) of diisobutylaluminum hydride in hexane at 0°C

and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated.

5 The residue was subjected to silica gel column chromatography, and 3-(3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (0.38 g, yield 92%) was obtained as a white powder from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).

10 1H -NMR ($CDCl_3$) δ : 1.33 (6H, d, $J=7.2$ Hz), 1.89-1.96 (2H, m), 2.57-2.61 (2H, m), 3.00-3.07 (1H, m), 3.73-3.78 (2H, m), 7.44 (1H, d, $J=7.6$ Hz), 7.88-7.91 (1H, m), 8.12 (1H, d, $J=8.4$ Hz), 8.30 (1H, s).

Reference Example 303

15 To a mixture of 2-benzyloxy-3-methylbenzaldehyde (37.00 g), methyl (methylthio)methyl sulfoxide (40.60 g) and tetrahydrofuran (400 ml) was added a 40% solution (8.00 ml) of benzyltrimethylammonium hydroxide in methanol at room temperature and the mixture was stirred at 65°C for 2 hours.

20 The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 2-[2-(benzyloxy)-3-methylphenyl]-1-(methylthio)vinyl methyl sulfoxide (47.00 g, yield 86%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

1H -NMR ($CDCl_3$) δ : 2.28 (3H, s), 2.32 (3H, s), 2.72 (3H, s), 4.81 (2H, s), 7.11 (1H, t, $J=7.6$ Hz), 7.23-7.26 (1H, m), 7.33-7.42 (3H, m), 7.48-7.51 (2H, m), 7.93-7.96 (1H, m), 8.02 (1H, s).

30 **Reference Example 304**

To a mixture of 2-benzyloxy-3-methoxybenzaldehyde (55.00 g), methyl (methylthio)methyl sulfoxide (57.10 g) and tetrahydrofuran (400 ml) was added a 40% solution (10.00 ml) of benzyltrimethylammonium hydroxide in methanol at room temperature and the mixture was stirred at 65°C for 2 hours.

The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 2-[2-(benzyloxy)-3-methoxyphenyl]-1-(methylthio)vinyl methyl sulfoxide (72.80 g, yield 91%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 2.68 (3H, s), 3.91 (3H, s), 5.03-5.04 (2H, m), 6.97 (1H, dd, J=8.0, 1.6 Hz), 7.10 (1H, t, J=8.0 Hz), 7.29-7.36 (3H, m), 7.44-7.46 (2H, m), 7.68 (1H, dd, J=8.0, 1.2 Hz), 7.92 (1H, s).

Reference Example 305

To a mixture of methyl 3-(3-tert-butyl-1H-pyrazol-4-yl)propanoate (0.75 g), 3-chloro-6-(trifluoromethyl)pyridazine (0.98 g) and N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.17 g), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propanoate (1.08 g, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:10, volume ratio).

¹H-NMR (CDCl₃) δ: 1.41 (9H, s), 2.72 (2H, t, J=7.5 Hz), 3.01 (2H, t, J=7.5 Hz), 3.73 (3H, s), 7.83 (1H, d, J=9.6 Hz), 8.28 (1H, d, J=9.6 Hz), 8.50 (1H, s).

Reference Example 306

To a solution of methyl 3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propanoate (1.08 g) in tetrahydrofuran (50 ml) was dropwise added a 0.93 M solution (8.1 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (0.66 g, yield 66%) was obtained as a 5 colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

1H -NMR ($CDCl_3$) δ : 1.41 (9H, s), 1.92-2.06 (2H, m), 2.77 (2H, t, $J=7.8$ Hz), 3.80 (2H, t, $J=6.0$ Hz), 7.83 (1H, d, $J=9.3$ Hz), 8.29 (1H, d, $J=9.3$ Hz), 8.52 (1H, s).

10 **Reference Example 307**

To a solution of methyl 3-(3-tert-butyl-1H-pyrazol-4-yl)propanoate (580 mg) in N,N-dimethylformamide (15 ml) was added 60% sodium hydride (132 mg), and the mixture was stirred at room temperature for 30 minutes. 2,5-Dibromopyridine (784 15 mg) was added to the reaction mixture and the mixture was stirred at 100°C for 1 hour. The reaction mixture was poured into water, neutralized with 2N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. 20 Ethanol (10 ml) and conc. sulfuric acid (0.05 ml) were added to the residue and the mixture was stirred at 70°C for 2 hours. The reaction mixture was poured into an aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried 25 ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). The crystals were recrystallized from hexane to give ethyl 3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4- 30 yl]propanoate (560 mg, yield 55%). melting point: 94-95°C.

Reference Example 308

To a solution of ethyl 3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-yl]propanoate (550 mg) in tetrahydrofuran (20 ml) was dropwise added a 1.0 M solution (5 ml) of 35 diisobutylaluminum hydride in hexane at 0°C and the mixture was

stirred at room temperature for 40 minutes. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated.

5 The residue was subjected to silica gel column chromatography, and 3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-yl]-1-propanol (455 mg, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (1H, t, $J=5.2$ Hz), 1.40 (9H, s), 1.9-2.05 (2H, m), 2.65-2.8 (2H, m), 3.7-3.85 (2H, m), 7.83 (1H, br s), 7.84 (1H, s), 8.2-8.22 (1H, m), 8.35-8.4 (1H, m).

Reference Example 309

To a solution of methyl 3-(3-tert-butyl-1H-pyrazol-4-yl)propanoate (0.75 g) in N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.17 g) and the mixture was stirred at room temperature for 30 minutes. 2,5-Dichloropyridine (0.80 g) was added to the reaction mixture and the mixture was stirred at 90°C for 4 hours. 0.1N Hydrochloric acid was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-yl]propanoate (0.95 g, yield 81%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (5:95, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (9H, s), 2.64-2.73 (2H, m), 2.94 (2H, m), 3.71 (3H, s), 7.69 (1H, dd, $J=8.8$, 2.6 Hz), 7.88 (1H, d, $J=8.8$ Hz), 8.20 (1H, s), 8.28 (1H, d, $J=2.6$ Hz).

Reference Example 310

To a solution of methyl 3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-yl]propanoate (0.95 g) in tetrahydrofuran (50 ml) was dropwise added a 0.93 M solution (8.0 ml) of diisobutylaluminum hydride in hexane at 0°C and the

mixture was stirred at 0°C for 1 hour. 1N Hydrochloric acid was poured into the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated.

5 The residue was subjected to silica gel column chromatography, and 3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-yl]-1-propanol (0.48 g, yield 55%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

10 1H -NMR ($CDCl_3$) δ : 1.34 (1H, t, $J=5.2$ Hz), 1.40 (9H, s), 1.87-2.02 (2H, m), 2.68-2.76 (2H, m), 3.72-3.82 (2H, m), 7.69 (1H, dd, $J=8.8$, 2.5 Hz), 7.89 (1H, d, $J=8.8$ Hz), 8.21 (1H, s), 8.28 (1H, d, $J=2.5$ Hz).

Reference Example 311

15 A mixture of sodium ethoxide (391 g) and diisopropyl ether (2 L) was added a mixture of diethyl succinate (500 g) and ethyl trifluoroacetate (836 g) at 60°C over 3 hours. The reaction mixture was stirred overnight at 60°C. The reaction mixture was poured into ice water (2 L) and conc. hydrochloric acid was added to adjust to pH 2. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give an oily substance (796.2 g). A mixture of the obtained oily substance (796.2 g) and 40% aqueous sulfuric acid solution (3.3 L) was refluxed overnight. The reaction mixture was added to ice (2 kg), and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give an oily substance (401.6 g). To a mixture of the obtained oily substance (401.6 g) and ethanol (1.5 L) was added hydrazine monohydrate (200 ml) at 0°C and the mixture was refluxed overnight. The reaction mixture was concentrated and water was added to the residue. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue 35 was subjected to silica gel column chromatography, and 4,5-

dihydro-6-(trifluoromethyl)-3-pyridazinone (209.57 g, yield 44%) was obtained as yellow crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). melting point: 94-95°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.57-2.85 (4H, m), 9.15 (1H, brs).

Reference Example 312

A mixture of 4,5-dihydro-6-(trifluoromethyl)-3-pyridazinone (90.0 g), bromine (30.5 ml) and acetic acid (270 ml) was stirred at 80°C for 1 hour. Ice water (500 ml) was 10 added to the reaction mixture. The precipitated crystals were collected by filtration, washed with aqueous sodium hydrogen carbonate and water and dried to give 6-(trifluoromethyl)-3-pyridazinone (58.74 g, yield 66%) as white crystals. melting point: 129-130°C.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 7.14 (1H, dd, $J=9.9$, 0.5 Hz), 7.54 (1H, d, $J=10.0$ Hz), 12.64 (1H, brs).

Reference Example 313

A mixture of 6-(trifluoromethyl)-3-pyridazinone (1.41 g), thionyl chloride (1.5 ml) and N,N-dimethylformamide (0.3 ml) 20 was refluxed for 2 hours. Excess thionyl chloride was evaporated under reduced pressure and aqueous sodium hydrogen carbonate was added. The mixture was extracted with diethyl ether. The diethyl ether layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was 25 subjected to silica gel column chromatography, and 3-chloro-6-(trifluoromethyl)pyridazine (1.45 g, yield 92%) was obtained as white crystals from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). melting point: 51-52°C.

30 $^1\text{H-NMR}$ (CDCl_3) δ : 7.75 (1H, dd, $J=8.7$, 0.6 Hz), 7.82 (1H, d, $J=9.0$ Hz).

Reference Example 314

A mixture of 3-methyl-2-butanone (10.7 ml) and bis(dimethylamino)methoxymethane (6.61 g) was heated under reflux for 8 hours. The reaction mixture was concentrated 35 under reduced pressure. Hydrazine monohydrate (5.80 g) and n-

butyl alcohol (29 ml) were added to the residue and the mixture was heated under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (1:1, volume ratio) to give 3-isopropyl-1H-pyrazole (4.26 g, yield 59%) as a colorless oil.
¹H-NMR (CDCl₃) δ: 1.30 (6H, d, J=6.9 Hz), 2.84-3.24 (1H, m), 6.10 (1H, d, J=2.0 Hz), 7.49 (1H, d, J=1.9 Hz), 10.3 (1H, br s).

10 Reference Example 315

In the same manner as in Reference Example 314, 3-(1-ethylpropyl)pyrazole (yield 91%) was obtained as a colorless oil.

¹H-NMR (CDCl₃) δ: 0.84 (6H, t, J=7.4 Hz), 1.5-1.8 (4H, m), 2.5-2.6 (1H, m), 6.06 (1H, d, J=1.9 Hz), 7.52 (1H, d, J=1.9 Hz).

Reference Example 316

To a mixture of 3-isopropyl-1H-pyrazole (3.74 g), 2-chloro-5-trifluoromethylpyridine (6.17 g) and N-methylpyrrolidone (18.7 ml) was added NaOH (trademark: Tosoh pearl, 2.03 g) while stirring the mixture at room temperature. After reaction as it was for 9 hours, water (38 ml) and 6N hydrochloric acid (85 ml) were added, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane and then with toluene to give 2-(3-isopropyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (6.94 g, yield 80%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.33 (6H, d, J=7.0 Hz), 3.0-3.2 (1H, m), 6.34 (1H, d, J=2.5 Hz), 7.97 (1H, dd, J=8.7, 2.1 Hz), 8.05 (1H, d, J=8.7 Hz), 8.47 (1H, d, J=2.5 Hz), 8.6-8.7 (1H, m).

Reference Example 317

In the same manner as in Reference Example 316, 2-[3-(1-ethylpropyl)-1H-pyrazol-1-yl]-5-(trifluoromethyl)pyridine (yield 61%) was obtained as a colorless oil.

¹H-NMR (CDCl₃) δ: 0.87 (6H, t, J=7.4 Hz), 1.5-1.8 (4H, m), 2.6-2.7 (1H, m), 6.28 (1H, d, J=2.7 Hz), 7.97 (1H, dd, J=8.7, 2.2 Hz), 8.07 (1H, d, J=8.7 Hz), 8.49 (1H, d, J=2.7 Hz), 8.6-8.7 (1H, m).

⁵ Reference Example 318

A solution of 2-(3-isopropyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (1.55 g) in acetonitrile (31 ml) was added iodine (924 mg), then diammonium cerium(IV) nitrate (2.00 g) while stirring the mixture at room temperature, and ¹⁰ the mixture was reacted as it was for 5 hours. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous ¹⁵ sodium thiosulfate solution, dried (magnesium sulfate) and concentrated under reduced pressure to give 2-(4-iodo-3-isopropyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (2.19 g, yield 95%) as crystals.

¹H-NMR (CDCl₃) δ: 1.38 (6H, d, J=6.9 Hz), 3.0-3.2 (1H, m), 7.99 (1H, dd, J=8.7, 2.0 Hz), 8.05 (1H, d, J=8.7 Hz), 8.57 (1H, s), ²⁰ 8.6-8.7 (1H, m).

Reference Example 319

In the same manner as in Reference Example 318, 2-[3-(1-ethylpropyl)-4-iodo-1H-pyrazol-1-yl]-5-(trifluoromethyl)pyridine (yield 95%) was obtained as a ²⁵ colorless oil.

¹H-NMR (CDCl₃) δ: 0.87 (6H, t, J=7.4 Hz), 1.6-1.9 (4H, m), 2.7-2.8 (1H, m), 7.99 (1H, dd, J=8.7, 2.1 Hz), 8.06 (1H, d, J=8.7 Hz), 8.59 (1H, s), ³⁰ 8.63 (1H, d, J=2.1 Hz).

Reference Example 320

A mixture of 2-(4-iodo-3-isopropyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (841 mg), palladium acetate (49.6 mg), triphenylphosphine (116 mg), potassium acetate (434 mg), benzyltriethylammonium chloride (504 mg), methyl acrylate (0.793 ml) and N-methylpyrrolidone (8.41 ml) was stirred at ³⁵

room temperature under a nitrogen stream for 1 hour. The mixture was heated to outer temperature of 90°C for 20 minutes and an insoluble material was filtered off and washed with ethyl acetate. Water was added to the filtrate, and the 5 mixture was extracted with ethyl acetate. The organic layers were combined, washed with water and dried (magnesium sulfate). The mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (95:5, volume ratio) to 10 give methyl 3-{3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}-2-propenoate (653 mg, yield 87%) as crystals.

¹H-NMR (CDCl₃) δ: 1.37 (6H, d, J=6.9 Hz), 3.1-3.3 (1H, m), 3.81 (3H, s), 6.29 (1H, d, J=16.0 Hz), 7.64 (1H, d, J=16.0 Hz), 15 8.00 (1H, dd, J=8.7, 2.1 Hz), 8.10 (1H, d, J=8.7 Hz), 8.6-8.7 (1H, m), 8.75 (1H, s).

Reference Example 321

In the same manner as in Reference Example 320 except that ethyl acrylate was used instead of methyl acrylate, ethyl 20 3-{3-(2-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}-2-propenoate (yield 70%) was obtained as a colorless oil.

¹H-NMR (CDCl₃) δ: 0.87 (6H, t, J=7.4 Hz), 1.34 (3H, t, J=7.1 Hz), 1.6-1.9 (4H, m), 2.7-2.8 (1H, m), 4.26 (2H, q, J=7.1 Hz), 25 6.31 (1H, d, J=16.0 Hz), 7.61 (1H, d, J=16.0 Hz), 8.01 (1H, dd, J=8.7, 2.2 Hz), 8.10 (1H, d, J=8.7 Hz), 8.6-8.7 (1H, m), 8.77 (1H, s).

Reference Example 322

To a mixture of 3-isopropyl-1H-pyrazole (167 g), 30 diammonium cerium(IV) nitrate (497 g) and acetonitrile (1200 ml) was added iodine (230 g) at 0°C and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium 35 thiosulfate solution and saturated brine, dried (MgSO₄) and

concentrated to give 4-iodo-3-isopropyl-1H-pyrazole (254 g, yield 71%) as a dark brown oily substance.

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, J=6.9 Hz), 3.00-3.17 (1H, m), 7.52 (1H, s).

5 Reference Example 323

To a mixture of 4-iodo-3-isopropyl-1H-pyrazole (254 g), potassium tert-butoxide (156 g) and tetrahydrofuran (1000 ml) was added benzyl bromide (134 ml) and the mixture was stirred at 0°C and at room temperature overnight. Water was added to 10 the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-4-iodo-3-isopropyl-1H-pyrazole (320 g, yield 92%) was obtained 15 as a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, J=6.9 Hz), 2.94-3.04 (1H, m), 5.24 (2H, s), 7.01-7.07 (1H, m), 7.16-7.36 (5H, m).

Reference Example 324

To a mixture of 3-isopropyl-1H-pyrazole (92.5 g), potassium tert-butoxide (123 g) and tetrahydrofuran (840 ml) was added benzyl bromide (125 ml) at 0°C and the mixture was stirred at room temperature for 5 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-3-isopropyl-1H-pyrazole (114 g, yield 68%) was obtained as a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 1.27 (6H, d, J=7.2 Hz), 2.96-3.07 (1H, m), 5.26 (2H, s), 6.06-6.09 (1H, m), 7.02-7.07 (1H, m), 7.14-7.36 (5H, m).

Reference Example 325

35 To a mixture of 1-benzyl-4-iodo-3-isopropyl-1H-pyrazole

(110 g), palladium(II) acetate (7.56 g), triphenylphosphine (17.7 g), benzyltriethylammonium chloride (76.8 g), methyl acrylate (121 ml) and 1-methyl-2-pyrrolidone (1000 ml) was added sodium acetate (55.3 g) at room temperature and the mixture was stirred overnight at 80°C under an argon atmosphere. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Ethyl acetate was added to the residue, and an insoluble material was removed by filtration. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, saturated aqueous sodium thiosulfate solution and water, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (E)-3-(1-benzyl-3-isopropyl-1H-pyrazol-4-yl)-2-propenoate (81.1 g, yield 81%) was obtained as a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (6H, d, $J=6.9$ Hz), 3.08-3.21 (1H, m), 3.75 (3H, s), 5.25 (2H, s), 6.02 (1H, d, $J=16.2$ Hz), 7.04-7.09 (1H, m), 7.20-7.38 (4H, m), 7.46 (1H, s), 7.59 (1H, d, $J=16.2$ Hz).

Reference Example 326

To a mixture of methyl (E)-3-(1-benzyl-3-isopropyl-1H-pyrazol-4-yl)-2-propenoate (52.5 g), 5% palladium-carbon (100 g) and ethanol (500 ml) was added formic acid (250 ml), and the mixture was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and palladium-carbon was removed by filtration. The filtrate was concentrated and the residue was diluted with ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried (MgSO_4) and concentrated to give methyl 3-(3-isopropyl-1H-pyrazol-4-yl)propanoate (31.5 g, yield 87%) as a pale-yellow oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (6H, d, $J=7.2$ Hz), 2.54-2.61 (2H, m),

2.74-2.82 (2H, m), 2.98-3.13 (1H, m), 3.68 (3H, s), 7.33 (1H, s).

Reference Example 327

To a mixture of methyl 3-(3-isopropyl-1H-pyrazol-4-yl)propanoate (70.0 g), 3-chloro-6-(trifluoromethyl)pyridazine (71.6 g) and N,N-dimethylformamide (700 ml) was added sodium hydride (60% in oil, 16.4 g) at 0°C, and the mixture was stirred at said temperature for 2 hours. The reaction solution was poured into dilute hydrochloric acid and the organic layer was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propanoate (92.6 g, yield 76%) was obtained as a pale-yellow solid from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (6H, d, $J=7.2$ Hz), 2.64-2.71 (2H, m), 2.82-2.89 (2H, m), 3.00-3.10 (1H, m), 3.71 (3H, s), 7.84 (1H, d, $J=9.0$ Hz), 8.29 (1H, d, $J=9.0$ Hz), 8.49 (1H, s).

Reference Example 328

To a solution of methyl 3-(3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)propanoate (92.6 g) in tetrahydrofuran (400 ml) was dropwise added a 1.5 M solution (396 ml) of diisobutylaluminum hydride in toluene at 0°C and the mixture was stirred at said temperature for 30 minutes. Sodium sulfate 10 hydrate (87.0 g) was added to the reaction mixture at 0°C and the mixture was stirred overnight at room temperature. Dilute hydrochloric acid was added to the mixture and the mixture was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). The obtained solid was washed with hexane to give 3-{3-isopropyl-1-[6-

(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (57.8 g, yield 68%) as a white solid.

¹H-NMR (CDCl₃) δ: 1.33 (6H, d, J=6.6 Hz), 1.42 (1H, t, J=5.1 Hz), 1.84-2.01 (2H, m), 2.63 (2H, t, J=7.9 Hz), 3.05 (1H, 5 septet, J=6.8 Hz), 3.77 (2H, q, J=5.7 Hz), 7.83 (1H, d, J=9.0 Hz), 8.29 (1H, d, J=9.0 Hz), 8.50 (1H, s).

Reference Example 329

To a solution of 4-(benzyloxy)-2-hydroxybenzaldehyde (16.5 g) in ethylene glycol (90 ml) were added potassium hydroxide (12.2 g) and hydrazine monohydrate (10.6 ml) at room temperature and the mixture was stirred at 120°C for 3 hours and at 199°C overnight. The reaction solution was cooled to room temperature and 2N hydrochloric acid (110 ml) was added. The mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried (MgSO₄) and concentrated to give 5-(benzyloxy)-2-methylphenol (14.8 g, yield 95%) as a brown oily substance.

¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 5.01 (2H, s), 6.43-6.51 (2H, m), 6.99 (1H, d, J=8.4 Hz), 7.27-7.43 (5H, m).

20 Reference Example 330

To a mixture of 5-(benzyloxy)-2-methylphenol (14.8 g), methyl chloromethyl ether (7.82 ml) and tetrahydrofuran (250 ml) was added sodium hydride (60% in oil, 4.12 g) at 0°C and the mixture was stirred at room temperature for 5 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and 4-(benzyloxy)-2-(methoxymethoxy)-1-methylbenzene (12.8 g, yield 72%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 3.47 (3H, s), 5.02 (2H, s), 5.16 (2H, s), 6.53 (1H, dd, J=2.4, 8.4 Hz), 6.75 (1H, d, J=2.4 Hz), 7.02 (1H, d, J=8.4 Hz), 7.28-7.45 (5H, m).

35 Reference Example 331

A mixture of 4-(benzyloxy)-2-(methoxymethoxy)-1-methylbenzene (12.8 g), 5% palladium-carbon (2.56 g) and ethanol (200 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by 5 filtration and the filtrate was concentrated to give 3-(methoxymethoxy)-4-methylphenol (7.98 g, yield 96%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 2.15 (3H, s), 3.48 (3H, s), 5.16 (2H, s), 6.39 (1H, dd, J=2.4, 8.1 Hz), 6.60 (1H, d, J=2.4 Hz), 6.96 10 (1H, d, J=8.1 Hz).

Reference Example 332

A mixture of 3-(methoxymethoxy)-4-methylphenol (7.98 g), ethyl 2-bromoisobutyrate (50 ml), potassium carbonate (48.7 g) and N,N-dimethylformamide (200 ml) was stirred at 80°C for 2 15 hours. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous ammonium chloride solution and saturated brine, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-[3-(methoxymethoxy)-4-methylphenoxy]-2-methylpropanoate (10.6 g, yield 79%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

¹H-NMR (CDCl₃) δ: 1.27 (3H, t, J=6.9 Hz), 1.57 (6H, s), 2.16 25 (3H, s), 3.46 (3H, s), 4.23 (2H, q, J=6.9 Hz), 5.13 (2H, s), 6.36 (1H, dd, J=2.4, 8.1 Hz), 6.65 (1H, d, J=2.4 Hz), 6.95 (1H, d, J=8.1 Hz).

Reference Example 333

To a solution of ethyl 2-[3-(methoxymethoxy)-4-methylphenoxy]-2-methylpropanoate (10.6 g) in ethanol (150 ml) was added several drops of conc. hydrochloric acid, and the mixture was stirred while heating under reflux for 4 hours. The reaction solution was cooled to room temperature, and concentrated. The residue was subjected to silica gel column 35 chromatography, and ethyl 2-(3-hydroxy-4-methylphenoxy)-2-

methylpropanoate (7.56 g, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:17, volume ratio).

¹H-NMR (CDCl₃) δ: 1.26 (3H, t, J=7.2 Hz), 1.57 (6H, s), 2.16
5 (3H, s), 4.23 (2H, q, J=7.2 Hz), 4.77 (1H, s), 6.30-6.37 (2H,
m), 6.93 (1H, d, J=7.8 Hz).

Reference Example 334

To a mixture of 2',4'-dihydroxyacetophenone (25.0 g), potassium carbonate (24.9 g) and acetone (500 ml) was dropwise
10 added benzyl bromide (21.4 ml) at 0°C and the mixture was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated to give a pale-yellow solid. The obtained solid was recrystallized from ethanol to give 1-[4-(benzyloxy)-2-
15 hydroxyphenyl]ethanone (33.8 g, yield 85%) as colorless crystals. melting point: 107-108°C.

Reference Example 335

To a solution of 1-[4-(benzyloxy)-2-hydroxyphenyl]ethanone (32.8 g) in tetrahydrofuran (400 ml)
20 were added methyl chloromethyl ether (24.8 ml) and potassium tert-butoxide (36.6 g) at 0°C and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried (MgSO₄) and
25 concentrated. The residue was subjected to silica gel column chromatography, and 1-[4-(benzyloxy)-2-(methoxymethoxy)phenyl]ethanone (18.6 g, yield 48%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

³⁰ ¹H-NMR (CDCl₃) δ: 2.61 (3H, s), 3.51 (3H, s), 5.10 (2H, s), 5.26 (2H, s), 6.65 (1H, dd, J=2.2, 8.8 Hz), 6.79 (1H, d, J=2.2 Hz), 7.32-7.48 (5H, m), 7.81 (1H, d, J=8.8 Hz).

Reference Example 336

To a solution of 1-[4-(benzyloxy)-2-(methoxymethoxy)phenyl]ethanone (10.0 g) in ethylene glycol
35

(50 ml) were added potassium hydroxide (5.88 g) and hydrazine monohydrate (5.11 ml) at room temperature and the mixture was stirred at 120°C for 2 hours and at 199°C overnight. The reaction solution was cooled to room temperature, neutralized with 2N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 5-(benzyloxy)-2-ethylphenol (4.43 g, yield 56%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (3H, t, $J=7.5$ Hz), 2.56 (2H, q, $J=7.5$ Hz), 4.68 (1H, s), 5.01 (2H, s), 6.44 (1H, d, $J=2.4$ Hz), 6.51 (1H, dd, $J=2.4, 8.4$ Hz), 7.01 (1H, d, $J=8.4$ Hz), 7.27-7.44 (5H, m).

¹⁵ **Reference Example 337**

To a solution of 3-(benzyloxy)-4-methoxybenzaldehyde (10.0 g) in methylene chloride (200 ml) was added m-chloroperbenzoic acid (24.4 g) at 0°C and the mixture was stirred at said temperature for 2 hours. To a reaction solution was added a saturated aqueous sodium thiosulfate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried (MgSO_4) and concentrated. A mixture of the residue, a 2N ammonia-methanol solution (100 ml) and methanol (100 ml) was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was subjected to silica gel column chromatography and 3-(benzyloxy)-4-methoxyphenol (8.78 g, yield 92%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.84 (3H, s), 4.51 (1H, s), 5.12 (2H, s), 6.35 (1H, dd, $J=3.0, 8.8$ Hz), 6.47 (1H, d, $J=3.0$ Hz), 6.76 (1H, d, $J=8.8$ Hz), 7.28-7.50 (5H, m).

Reference Example 338

³⁵ To a solution of 5-(benzyloxy)-2-ethylphenol (4.43 g) in

tetrahydrofuran (90 ml) was added sodium hydride (60% in oil, 1.16 g) at room temperature and the mixture was stirred for 30 minutes. Methyl chloromethyl ether (2.21 ml) was added at room temperature, and the mixture was stirred overnight. Water was 5 added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 4-(benzyloxy)-1-ethyl-2-(methoxymethoxy)benzene (4.57 g, yield 10 86%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.17 (3H, t, $J=7.4$ Hz), 2.59 (2H, q, $J=7.4$ Hz), 3.48 (3H, s), 5.02 (2H, s), 5.17 (2H, s), 6.56 (1H, dd, $J=2.6$, 8.4 Hz), 6.77 (1H, d, $J=2.6$ Hz), 7.05 (1H, d, $J=8.4$ Hz), 15 7.30-7.48 (5H, m).

Reference Example 339

A mixture of 3-(benzyloxy)-4-methoxyphenol (8.78 g), ethyl 2-bromoisobutyrate (28.0 ml), potassium carbonate (26.3 g) and N,N-dimethylformamide (190 ml) was stirred at 80°C for 5 20 hours. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-[3-(benzyloxy)- 25 4-methoxyphenoxy]-2-methylpropanoate (11.0 g, yield 83%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (3H, t, $J=7.0$ Hz), 1.47 (6H, s), 3.84 (3H, s), 4.18 (2H, q, $J=7.0$ Hz), 5.10 (2H, s), 6.41 (1H, dd, $J=2.6$, 8.8 Hz), 6.54 (1H, d, $J=2.6$ Hz), 6.74 (1H, d, $J=8.8$ Hz), 30 7.24-7.46 (5H, m).

Reference Example 340

A mixture of 4-(benzyloxy)-1-ethyl-2-(methoxymethoxy)benzene (4.57 g), 5% palladium-carbon (1.00 g) 35 and ethanol (90 ml) was stirred overnight at room temperature

under a hydrogen atmosphere. Palladium–carbon was removed by filtration and the filtrate was concentrated to give 4-ethyl-3-(methoxymethoxy)phenol (3.06 g, quantitative) as a pale-yellow oily substance.

⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 1.16 (3H, t, $J=7.4$ Hz), 2.58 (2H, q, $J=7.4$ Hz), 3.48 (3H, s), 4.69 (1H, s), 5.17 (2H, s), 6.42 (1H, dd, $J=2.6$, 8.0 Hz), 6.62 (1H, d, $J=2.6$ Hz), 7.00 (1H, d, $J=8.0$ Hz).

Reference Example 341

¹⁰ A mixture of ethyl 2-[3-(benzyloxy)-4-methoxyphenoxy]-2-methylpropanoate (11.0 g), 5% palladium–carbon (2.19 g) and ethanol (160 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium–carbon was removed by filtration and the filtrate was concentrated. The residue was ¹⁵ subjected to silica gel column chromatography, and ethyl 2-(3-hydroxy-4-methoxyphenoxy)-2-methylpropanoate (8.00 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

¹ $^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (3H, t, $J=7.2$ Hz), 1.54 (6H, s), 3.84 (3H, s), 4.24 (2H, q, $J=7.2$ Hz), 5.57 (1H, s), 6.37 (1H, dd, $J=3.0$, 8.7 Hz), 6.54 (1H, d, $J=3.0$ Hz), 6.69 (1H, d, $J=8.7$ Hz).

Reference Example 342

²⁵ A mixture of 4-ethyl-3-(methoxymethoxy)phenol (3.06 g), ethyl 2-bromoisobutyrate (9.86 ml), potassium carbonate (9.28 g) and N,N-dimethylformamide (85 ml) was stirred overnight at 80°C. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, ³⁰ dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-[4-ethyl-3-(methoxymethoxy)phenoxy]-2-methylpropanoate (4.93 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

³⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 1.16 (3H, t, $J=7.4$ Hz), 1.27 (3H, t, $J=7.4$

Hz), 1.58 (6H, s), 2.57 (2H, q, J=7.4 Hz), 3.46 (3H, s), 4.24 (2H, q, J=7.4 Hz), 5.14 (2H, s), 6.39 (1H, dd, J=2.6, 8.0 Hz), 6.66 (1H, d, J=2.6 Hz), 6.97 (1H, d, J=8.0 Hz).

Reference Example 343

5 To a solution of ethyl 2-[4-ethyl-3-(methoxymethoxy)phenoxy]-2-methylpropanoate (4.93 g) in ethanol (85 ml) was added several drops of conc. hydrochloric acid and the mixture was stirred overnight while heating under reflux. The reaction solution was cooled to room temperature
10 and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-(4-ethyl-3-hydroxyphenoxy)-2-methylpropanoate (3.72 g, yield 89%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (3:37, volume ratio).
15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.20 (3H, t, J=7.5 Hz), 1.26 (3H, t, J=7.2 Hz), 1.57 (6H, s), 2.55 (2H, q, J=7.5 Hz), 4.24 (2H, q, J=7.2 Hz), 4.75 (1H, s), 6.33-6.39 (2H, m), 6.96 (1H, d, J=8.1 Hz).

Reference Example 344

To a mixture of 1-benzyl-3-isopropyl-1*H*-pyrazole (224 g),
20 diammonium cerium(IV) nitrate (368 g) and acetonitrile (1000 ml) was added iodine (171 g) at 0°C and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
25 thiosulfate solution and saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-4-iodo-3-isopropyl-1*H*-pyrazole (340 g, yield 93%) was obtained as a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume
30 ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (6H, d, J=6.9 Hz), 2.94-3.04 (1H, m), 5.24 (2H, s), 7.01-7.07 (1H, m), 7.16-7.36 (5H, m).

Reference Example 345

A mixture of 2-{3-(1-ethylpropyl)-4-iodo-1*H*-pyrazol-1-
35 yl}-5-(trifluoromethyl)pyridine (4.09 g), palladium acetate

(112 mg), triphenylphosphine (262 mg), sodium carbonate (2.12 g), benzyltriethylammonium chloride (2.28 g), allyl alcohol (1.02 ml), water (4.09 ml) and N,N-dimethylformamide (40.9 ml) was stirred at room temperature for 1 hour under a nitrogen stream. The mixture was heated at an outer temperature of 60°C for 8 hours. The insoluble material was filtered off and washed with ethyl acetate. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous sodium thiosulfate solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (9:1, volume ratio) to give 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propanal (1.17 g, yield 35%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.7-0.9 (6H, m), 1.6-1.9 (4H, m), 2.5-2.6 (1H, m), 2.7-2.8 (4H, m), 7.9-8.1 (2H, m), 8.27 (1H, s), 8.5-8.6 (1H, m), 9.86 (1H, s).

Reference Example 346

To a solution of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propanal (1.15 g) in methanol (25.2 ml) was added sodium borohydride (492 mg) with stirring under ice-cooling under a nitrogen stream. After stirring at said temperature for 0.5 hour, water (50 ml) and 6N hydrochloric acid (13 mmol) were added, and the mixture was stirred for 1 hour. The mixture was neutralized with 2N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layers were combined, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (4:1, volume ratio) to give 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propan-1-ol (669 mg, yield 58%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (6H, t, $J=7.4$ Hz), 1.6-1.9 (6H, m), 2.5-

2.7 (3H, m), 3.6-3.8 (2H, m), 7.94 (1H, dd, J=8.7, 2.2 Hz),
8.03 (1H, d, J=8.7 Hz), 8.28 (1H, s), 8.5-8.6 (1H, m).

Reference Example 347

A mixture of 2-(4-iodo-3-isopropyl-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (7.62 g), palladium acetate (225 mg), triphenylphosphine (525 mg), sodium hydrogen carbonate (3.28 g), benzyltriethylammonium chloride (4.56 g), allyl alcohol (2.05 ml), water (7.62 ml) and N-methylpyrrolidone (76.2 ml) was stirred at room temperature for 1 hour under a nitrogen stream. The mixture was heated at an outer temperature of 60°C for 6 hours. The insoluble material was filtered off and washed with ethyl acetate. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous sodium thiosulfate solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (9:1, volume ratio) to give 3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propanal (3.93 g, yield 63%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.34 (6H, d, J=6.9 Hz), 2.7-3.1 (5H, m), 7.95 (1H, dd, J=8.7, 2.2 Hz), 8.03 (1H, d, J=8.7 Hz), 8.26 (1H, s), 8.60 (1H, d, J=2.0 Hz), 9.86 (1H, s).

Reference Example 348

To a solution of 3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propanal (3.89 g) in methanol (77.8 ml) was added sodium borohydride (1.66 g) with stirring under ice-cooling under a nitrogen stream. After stirring at said temperature for 1 hour, water (50 ml) and 6N hydrochloric acid (44 mmol) were added, and the mixture was stirred for 1 hour. The precipitated crystals were collected by filtration to give 3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propan-1-ol (3.73 g, yield 95%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (6H, d, J=6.9 Hz), 1.8-2.0 (2H, m), 2.60

(2H, t, J=7.9 Hz), 3.0-3.1 (1H, m), 3.75 (2H, t, J=6.3 Hz), 7.94 (1H, dd, J=8.7, 2.2 Hz), 8.03 (1H, d, J=8.7 Hz), 8.28 (1H, s), 8.6-8.7 (1H, m).

Reference Example 349

5 To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propan-1-ol (470 mg) and toluene (9.4 ml) were added triethylamine (258 mg) and then methanesulfonyl chloride (258 mg) with stirring under ice-cooling. After stirring at room temperature for 30
10 minutes, water (10 ml) was added, and the mixture was extracted with toluene. The organic layer was washed with saturated brine and the mixture was concentrated under reduced pressure. o-Vanillin (342 mg), potassium carbonate (353 mg), ethanol (4.7 ml) and toluene (4.7 ml) were added to the
15 residue and the mixture was reacted under reflux for 5.5 hours. After completion of the reaction, water (10 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with 3N aqueous sodium hydroxide solution and saturated aqueous sodium
20 hydrogen carbonate in this order, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (9:1, volume ratio) to give 2-(3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-
25 yl)propoxy)-3-methoxybenzaldehyde (450 mg, yield 67%) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.34 (6H, d, J=6.9 Hz), 2.1-2.2 (2H, m), 2.73 (2H, t, J=7.7 Hz), 3.0-3.1 (1H, m), 3.90 (3H, s), 4.22 (2H, t, J=6.3 Hz), 7.1-7.2 (2H, m), 7.4-7.5 (1H, m), 7.95 (1H, dd, J=8.7, 2.2 Hz), 8.04 (1H, d, J=8.7 Hz), 8.33 (1H, s), 8.6-8.7 (1H, m), 10.5 (1H, s).

Reference Example 350

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propan-1-ol (470 mg) and tetrahydrofuran (13.8 ml) were added

triethylamine (0.927 ml) and then methanesulfonyl chloride (0.511 ml) with stirring under ice-cooling. After stirring under ice-cooling for 1.5 hours, water was added, and the mixture was extracted with ethyl acetate. The organic layer 5 was washed with saturated brine and concentrated under reduced pressure. o-Vanillin (1.21 g), potassium carbonate (1.09 g), acetonitrile (27.6 ml) were added to the residue and the mixture was reacted under reflux for 2.5 hours. After completion of the reaction, water was added to the reaction 10 mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with 3N aqueous sodium hydroxide solution and water in this order, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Hexane was added to the residue to give 2-(3-{3-isopropyl-1-[5- 15 (trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxybenzaldehyde (1.21 g) as crystals. The mother liquor was concentrated, subjected to silica gel column chromatography and eluted with hexane-ethyl acetate (9:1, volume ratio) to give 2-(3-{3-isopropyl-1-[5- 20 (trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxybenzaldehyde (401 mg, total yield 77%) as colorless crystals.

¹H-NMR (CDCl₃) δ: 1.34 (6H, d, J=6.9 Hz), 2.1-2.2 (2H, m), 2.73 (2H, t, J=7.7 Hz), 3.0-3.1 (1H, m), 3.90 (3H, s), 4.22 (2H, t, J=6.3 Hz), 7.1-7.2 (2H, m), 7.4-7.5 (1H, m), 7.95 (1H, dd, J=8.7, 2.2 Hz), 8.04 (1H, d, J=8.7 Hz), 8.33 (1H, s), 8.6-8.7 (1H, m), 10.5 (1H, s).

Reference Example 351

In the same manner as in Reference Example 350, 2-(3-{3- 30 (1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxybenzaldehyde (yield 67%) was obtained.

¹H-NMR (CDCl₃) δ: 1.34 (6H, t, J=7.4 Hz), 1.5-1.8 (4H, m), 2.0-2.2 (2H, m), 2.3-2.8 (3H, m), 3.90 (3H, s), 4.1-4.3 (2H, s), 35 7.1-7.2 (2H, m), 7.4-7.5 (1H, m), 7.90-8.00 (2H, m), 8.33 (1H,

s), 8.6-8.7 (1H, m), 10.5 (1H, s).

Example 1

A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 4-hydroxyphenylacetate (500 mg), potassium carbonate (440 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]propoxy)phenyl]acetic acid (300 mg, yield 25%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 127-128°C.

²⁵ $^1\text{H-NMR}$ (CDCl_3) δ : 2.18-2.32 (2H, m), 2.98-3.10 (2H, m), 3.60 (2H, s), 3.98-4.08 (2H, m), 6.37 (1H, s), 6.82-6.90 (2H, m), 7.15-7.24 (2H, m), 7.66-7.75 (2H, m), 7.86-7.94 (2H, m).

Example 2

A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 4-hydroxybenzoate (460 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated

aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
10 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]propoxy)benzoic acid (840 mg, yield 72%). The crystals were recrystallized from
15 acetone-hexane. melting point: 221-222°C.

1H -NMR ($CDCl_3$) δ : 2.20-2.38 (2H, m), 3.00-3.14 (2H, m), 4.05-4.18 (2H, m), 6.39 (1H, s), 6.86-6.96 (2H, m), 7.64-7.74 (2H, m), 7.86-8.08 (4H, m).

Example 3

20 A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 3-hydroxyphenylacetate (500 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured
25 into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
30 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was
35 extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]propoxy)phenyl]acetic acid (630 mg, yield 52%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 126-127°C.
 1H -NMR ($CDCl_3$) δ : 2.16-2.34 (2H, m), 2.98-3.12 (2H, m), 3.63 (2H, s), 4.00-4.10 (2H, m), 6.38 (1H, s), 6.76-6.94 (3H, m), 7.18-7.32 (1H, m), 7.66-7.75 (2H, m), 7.86-7.96 (2H, m).

10 Example 4

A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide (520 mg), methyl 3-hydroxybenzoate (460 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]propoxy)benzoic acid (860 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 133-134°C.
 1H -NMR ($CDCl_3$) δ : 2.20-2.37 (2H, m), 3.02-3.14 (2H, m), 4.06-4.17 (2H, m), 6.39 (1H, s), 7.10-7.20 (1H, m), 7.34-7.44 (1H, m), 7.58-7.76 (4H, m), 7.86-7.96 (2H, m).

Example 5

A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide (520 mg), ethyl 3-(4-hydroxyphenyl)propionate (600 mg),
5 potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and
10 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol
15 (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected
20 by filtration to give 3-[4-(3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)propoxy]phenyl]propionic acid (520 mg, yield 42%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 174-175°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.16-2.34 (2H, m), 2.59-2.72 (2H, m), 2.84-
25 3.12 (4H, m), 3.98-4.08 (2H, m), 6.37 (1H, s), 6.78-6.88 (2H, m), 7.07-7.18 (2H, m), 7.66-7.76 (2H, m), 7.86-7.96 (2H, m).

Example 6

A mixture of 3-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-propyl methanesulfonate (1.04 g), sodium iodide
30 (500 mg), methyl salicylate (460 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
35 chloride solution, dried (MgSO_4) and concentrated. The residue

was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), 5 tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained 10 colorless crystals were collected by filtration to give 2-(3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)propoxy)benzoic acid (710 mg, yield 61%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

1H -NMR ($CDCl_3$) δ : 2.34-2.52 (2H, m), 3.03-3.16 (2H, m), 4.18-15 4.42 (2H, m), 6.43 (1H, s), 7.00-7.24 (2H, m), 7.50-7.64 (1H, m), 7.65-7.76 (2H, m), 7.85-7.96 (2H, m), 8.16-8.24 (1H, m).

Example 7

A mixture of 3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-propyl methanesulfonate (1.04 g), sodium iodide 20 (500 mg), methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (470 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was 25 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous 30 sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and 35 concentrated. The obtained colorless crystals were collected

by filtration to give 1-methyl-3-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)-1H-pyrazole-5-carboxylic acid (870 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 162-
5 163°C.

¹H-NMR (CDCl₃) δ: 2.16-2.34 (2H, m), 2.96-3.10 (2H, m), 4.04 (3H, s), 4.17-4.28 (2H, m), 6.30 (1H, s), 6.39 (1H, s), 7.67-7.77 (2H, m), 7.87-7.97 (2H, m).

Example 8

A mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (1.04 g), sodium iodide (500 mg), methyl 3-hydroxy-1-phenyl-1H-pyrazole-5-carboxylate (650 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 1-phenyl-3-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)-1H-pyrazole-5-carboxylic acid (1.16 g, yield 85%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 145-146°C.

¹H-NMR (CDCl₃) δ: 2.16-2.36 (2H, m), 2.96-3.10 (2H, m), 4.24-4.36 (2H, m), 6.40 (1H, s), 6.50 (1H, s), 7.36-7.47 (5H, m),
35 7.65-7.75 (2H, m), 7.84-7.94 (2H, m).

Example 9

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (500 mg), methyl 3-(4-hydroxyphenyl)propionate (370 mg), triphenylphosphine (530 mg)
5 and tetrahydrofuran (10 ml) was dropwise added a 40% solution of diethyl azodicarboxylate in toluene (900 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
10 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added and extracted
15 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenyl)propionic acid (620 mg,
20 yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 195-196°C.

1H -NMR ($CDCl_3$) δ : 2.39 (3H, s), 4.64 (2H, s), 4.94 (2H, s), 6.87-6.97 (4H, m), 7.96-8.06 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

Example 10

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (900 mg), methyl (4-hydroxyphenoxy)acetate (650 mg), triphenylphosphine (930 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.59 g) of diethyl azodicarboxylate in toluene at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (4-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)phenoxy)acetic acid (610 mg, yield 43%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.

1H -NMR ($CDCl_3$) δ : 2.39 (3H, s), 4.64 (2H, s), 4.94 (2H, s), 6.87-6.97 (4H, m), 7.96-8.06 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

15 Example 11

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (740 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (670 mg), triphenylphosphine (700 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.20 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-phenyl-3-(4-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)butoxy)-1H-pyrazol-5-yl]propionic acid (930 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 139-

140°C.

¹H-NMR (CDCl₃)δ: 1.76-2.06 (4H, m), 2.56-2.70 (2H, m), 2.84-3.02 (4H, m), 4.18-4.32 (2H, m), 5.68 (1H, s), 6.36 (1H, s), 7.28-7.48 (5H, m), 7.66-7.75 (2H, m), 7.85-7.94 (2H, m).

5 Example 12

A mixture of 4-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-butyl methanesulfonate (700 mg), sodium iodide (300 mg), methyl 4-hydroxybenzoate (290 mg), potassium carbonate (460 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(4-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)butoxy)benzoic acid (630 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 170-171°C.

¹H-NMR (CDCl₃)δ: 1.82-2.12 (4H, m), 2.86-2.98 (2H, m), 4.02-4.14 (2H, m), 6.36 (1H, s), 6.88-6.98 (2H, m), 7.66-7.76 (2H, m), 7.85-7.95 (2H, m), 8.00-8.10 (2H, m).

Example 13

To a mixture of 4-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-butanol (700 mg), methyl 4-hydroxyphenylacetate (400 mg), triphenylphosphine (660 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.10 g) of diethyl

azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]acetic acid (810 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.
 1H -NMR ($CDCl_3$) δ : 1.78-2.07 (4H, m), 2.83-2.95 (2H, m), 3.59 (2H, s), 3.94-4.06 (2H, m), 6.36 (1H, s), 6.79-6.91 (2H, m), 7.14-7.26 (2H, m), 7.64-7.76 (2H, m), 7.84-7.96 (2H, m).

20 Example 14

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 3-(4-hydroxyphenyl)propionate (440 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.25 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic acid (760 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131°C.

¹H-NMR (CDCl₃)δ: 1.80-2.04 (4H, m), 2.56-2.70 (2H, m), 2.82-2.98 (4H, m), 3.94-4.06 (2H, m), 6.36 (1H, s), 6.77-6.88 (2H, m), 7.07-7.17 (2H, m), 7.64-7.76 (2H, m), 7.85-7.96 (2H, m).

Example 15

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 2-(4-hydroxyphenoxy)-2-methylpropionate (500 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.10 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenoxy]propionic acid (860 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 103-104°C.

¹H-NMR (CDCl₃)δ: 1.53 (6H, s), 1.80-2.06 (4H, m), 2.86-2.98 (2H, m), 3.94-4.04 (2H, m), 6.36 (1H, s), 6.72-6.95 (4H, m), 7.66-7.75 (2H, m), 7.85-7.94 (2H, m).

Example 16

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 3-hydroxyphenylacetate

(420 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.13 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was 5 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol 10 (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were 15 collected by filtration to give [3-(4-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)butoxy]phenyl]acetic acid (800 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.
 1H -NMR ($CDCl_3$) δ : 1.80-2.08 (4H, m), 2.84-2.96 (2H, m), 3.62 20 (2H, s), 3.96-4.06 (2H, m), 6.36 (1H, s), 6.76-6.91 (3H, m), 7.18-7.30 (1H, m), 7.64-7.76 (2H, m), 7.85-7.96 (2H, m).

Example 17

To a mixture of 4-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]-1-butanol (700 mg), methyl 2-hydroxyphenylacetate 25 (420 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.10 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column 30 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N 35 Hydrochloric acid (5 ml) was added and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(4-[3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl]butoxy)phenyl]acetic acid (800 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.

¹H-NMR ($CDCl_3$) δ : 1.78-2.06 (4H, m), 2.78-2.92 (2H, m), 3.65 (2H, s), 3.96-4.07 (2H, m), 6.36 (1H, s), 6.80-6.96 (2H, m), 7.14-7.30 (2H, m), 7.64-7.74 (2H, m), 7.84-7.94 (2H, m).

Example 18

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (330 mg), methyl 2-(4-hydroxyphenoxy)-2-methylpropionate (250 mg), triphenylphosphine (310 mg) and tetrahydrofuran (7 ml) was dropwise added a 40% solution (550 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid (370 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 91-92°C.

¹H-NMR ($CDCl_3$) δ : 1.41 (3H, t, $J=7.0$ Hz), 1.54 (6H, s), 2.00-2.18 (2H, m), 2.54-2.66 (2H, m), 3.98 (2H, t, $J=6.2$ Hz), 4.35

(2H, q, J=7.0 Hz), 6.76–6.96 (4H, m), 7.81 (1H, d, J=8.8 Hz), 7.91 (1H, dd, J=2.0, 8.8 Hz), 8.18 (1H, s), 8.55 (1H, d, J=2.0 Hz).

Example 19

To a mixture of (3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (250 mg), ethyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (250 mg), triphenylphosphine (280 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (480 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(2-ethoxy-4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenyl)propionic acid (310 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 151–152°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (3H, t, J=7.0 Hz), 2.39 (3H, s), 2.60–2.71 (2H, m), 2.84–2.95 (2H, m), 4.01 (2H, q, J=7.0 Hz), 4.94 (2H, s), 6.45–6.54 (2H, m), 7.06–7.14 (1H, m), 7.94–8.08 (2H, m), 8.56 (1H, s), 8.61–8.68 (1H, m).

Example 20

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (1.10 g), methyl 3-(3-hydroxyphenyl)propionate (780 mg), triphenylphosphine (1.10 g) and tetrahydrofuran (15 ml) was dropwise added a 40% solution (1.75 g) of diethyl azodicarboxylate in toluene at room

temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (7 ml) and methanol (7 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (7 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic acid (1.26 g, yield 75%).

The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

1H -NMR ($CDCl_3$) δ : 1.80-2.08 (4H, m), 2.60-2.74 (2H, m), 2.85-3.00 (4H, m), 3.96-4.06 (2H, m), 6.36 (1H, s), 6.72-6.84 (3H, m), 7.15-7.27 (1H, m), 7.67-7.76 (2H, m), 7.86-7.95 (2H, m).

Example 21

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (570 mg), ethyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (480 mg), triphenylphosphine (550 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (950 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic acid (260 mg, yield 27%). The crystals were recrystallized
5 from ethyl acetate-hexane. melting point: 105-106°C.

¹H-NMR (CDCl₃)δ: 1.41 (3H, t, J=7.0 Hz), 1.78-2.08 (4H, m), 2.54-2.72 (2H, m), 2.82-2.97 (4H, m), 3.92-4.08 (4H, m), 6.32-6.44 (3H, m), 6.98-7.10 (1H, m), 7.66-7.76 (2H, m), 7.85-7.95 (2H, m).

10 **Example 22**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (410 mg), methyl 3-hydroxyphenylacetate (230 mg), triphenylphosphine (370 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (630 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
15 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
20 washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (330 mg, yield 56%). The
25 crystals were recrystallized from ethyl acetate-hexane.
30 melting point: 82-83°C.

¹H-NMR (CDCl₃)δ: 1.47 (6H, d, J=7.0 Hz), 2.02-2.21 (2H, m), 2.69 (2H, t, J=7.4 Hz), 2.94-3.12 (1H, m), 3.64 (2H, s), 4.05 (2H, t, J=6.0 Hz), 6.80-6.92 (3H, m), 7.19-7.30 (1H, m), 7.95 (1H, dd, J=1.8, 8.4 Hz), 8.05 (1H, d, J=8.4 Hz), 8.29 (1H, s),
35

8.57-8.64 (1H, m).

Example 23

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (380 mg), methyl 3-(3-hydroxyphenyl)propionate (220 mg), tributylphosphine (260 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (350 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl propionic acid (380 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 102-103°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (6H, d, $J=7.0$ Hz), 2.00-2.20 (2H, m), 2.62-2.76 (4H, m), 2.87-3.13 (3H, m), 4.05 (2H, t, $J=6.2$ Hz), 6.73-6.86 (3H, m), 7.15-7.26 (1H, m), 7.91-8.08 (2H, m), 8.27 (1H, s), 8.57-8.63 (1H, m).

Example 24

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (520 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (440 mg), tributylphosphine (510 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected

to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid (420 mg, yield 48%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 139-140°C.

¹⁵ 1H -NMR ($CDCl_3$) δ : 1.32 (6H, d, $J=7.0$ Hz), 2.00-2.20 (2H, m), 2.56-2.76 (4H, m), 2.88-3.12 (3H, m), 4.27 (2H, t, $J=6.0$ Hz), 5.72 (1H, s), 7.30-7.50 (5H, m), 7.95 (1H, dd, $J=2.6, 9.0$ Hz), 8.04 (1H, d, $J=9.0$ Hz), 8.27 (1H, s), 8.54-8.61 (1H, m).

Example 25

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (360 mg), tributylphosphine (530 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were

collected by filtration to give 3-[3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-1-methyl-1H-pyrazol-5-yl]propionic acid (630 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane.

5 melting point: 131-132°C.

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, J=7.0 Hz), 1.98-2.16 (2H, m), 2.58-3.12 (7H, m), 3.66 (3H, s), 4.16 (2H, t, J=6.2 Hz), 5.49 (1H s), 7.94 (1H, dd, J=1.8, 8.6 Hz), 8.04 (1H, d, J=8.6 Hz), 8.26 (1H, s), 8.56-8.62 (1H, m).

10 **Example 26**

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)-1-methyl-1H-pyrazole-5-carbaldehyde (1.10 g), ethyl diethylphosphonoacetate (690 mg) and N,N-dimethylformamide (15 ml), was added sodium hydride (60%, in oil, 120 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)-1-methyl-1H-pyrazol-5-yl)propenoate (1.03 g, yield 79%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

¹H-NMR (CDCl₃) δ: 1.33 (3H, t, J=7.0 Hz), 1.36 (6H, d, J=7.0 Hz), 3.07-3.24 (1H, m), 3.83 (3H, s), 4.27 (2H, q, J=7.0 Hz), 5.14 (2H, s), 5.95 (1H, s), 6.28 (1H, d, J=15.6 Hz), 7.48 (1H, d, J=15.6 Hz), 7.97 (1H, dd, J=2.2, 8.4 Hz), 8.07 (1H, d, J=8.4 Hz), 8.56 (1H, s), 8.60-8.66 (1H, m).

Example 27

A mixture of ethyl (E)-3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)-1-methyl-

1H-pyrazol-5-yl)propenoate (900 mg), 5% palladium-carbon (260 mg) and tetrahydrofuran (20 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. A mixture of the obtained crystal, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-yl)propionic acid (780 mg, yield 92%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 141-142°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (6H, d, $J=7.0$ Hz), 2.62-2.94 (4H, m), 3.06-3.24 (1H, m), 3.69 (3H, s), 5.10 (2H, s), 5.51 (1H, s), 7.98 (1H, dd, $J=2.2$, 9.2 Hz), 8.07 (1H, d, $J=9.2$ Hz), 8.53 (1H, s), 8.58-8.67 (1H, m).

Example 28

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (1.20 g), methyl 2-(3-hydroxyphenoxy)-2-methylpropionate (830 mg), tributylphosphine (1.60 g) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (2.01 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-⁵ 2-methylpropionic acid (1.32 g, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 101-102°C.

¹H-NMR ($CDCl_3$) δ : 1.32 (6H, d, $J=7.0$ Hz), 1.63 (6H, s), 2.00-2.18 (2H, m), 2.69 (2H, t, $J=7.2$ Hz), 2.94-3.12 (1H, m), 4.00¹⁰ (2H, t, $J=6.2$ Hz), 6.50-6.70 (3H, m), 7.11-7.24 (1H, m), 7.96 (1H, dd, $J=2.2$, 8.8 Hz), 8.06 (1H, d, $J=8.8$ Hz), 8.26 (1H, s), 8.54-8.63 (1H, m).

Example 29

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (550 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropionate (380 mg), tributylphosphine (730 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (910 mg) at room temperature and the mixture was stirred overnight. The reaction solution was¹⁵ concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol²⁰ (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were²⁵ collected by filtration to give 2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid (530 mg, yield 62%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

³⁵ ¹H-NMR ($CDCl_3$) δ : 1.41 (3H, t, $J=7.0$ Hz), 1.62 (6H, s), 1.96-

2.18 (2H, m), 2.62 (2H, t, J=7.0 Hz), 3.97 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.0 Hz), 6.48-6.68 (3H, m), 7.08-7.23 (1H, m), 7.84 (1H, d, J=8.8 Hz), 7.93 (1H, dd, J=2.6, 8.8 Hz), 8.16 (1H, s), 8.51-8.56 (1H, m).

5 Example 30

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (650 mg), methyl 3-hydroxyphenylacetate (380 mg), tributylphosphine (930 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (1.16 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (490 mg, yield 53%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 134-135°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (3H, t, J=7.2 Hz), 2.02-2.14 (2H, m), 2.60 (2H, t, J=7.2 Hz), 3.62 (2H, s), 4.01 (2H, t, J=6.3 Hz), 4.34 (2H, q, J=7.2 Hz), 6.78-6.88 (3H, m), 7.18-7.28 (1H, m), 7.80 (1H, d, J=8.7 Hz), 7.90 (1H, dd, J=2.4, 8.7 Hz), 8.17 (1H, s), 8.52-8.57 (1H, m).

Example 31

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (620 mg), methyl 2-hydroxyphenylacetate (340 mg), tributylphosphine (800 mg) and

tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (1.00 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (310 mg, yield 35%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 83-84°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, t, $J=7.0$ Hz), 2.00-2.18 (2H, m), 2.61 (2H, t, $J=7.0$ Hz), 3.68 (2H, s), 4.02 (2H, t, $J=6.2$ Hz), 4.34 (2H, q, $J=7.0$ Hz), 6.80-6.96 (2H, m), 7.14-7.28 (2H, m), 7.80 (1H, d, $J=8.8$ Hz), 7.90 (1H, dd, $J=2.2, 8.8$ Hz), 8.20 (1H, s), 8.49-8.56 (1H, m).

Example 32

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (500 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropionate (430 mg), triphenylphosphine (570 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (980 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium

hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was 5 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-(3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)phenoxy)propionic acid (600 mg, yield 71%). The 10 crystals were recrystallized from ethyl acetate-hexane. melting point: 152-153°C.

1H -NMR ($CDCl_3$) δ : 1.64 (6H, s), 2.38 (3H, s), 4.99 (2H, s), 6.52-6.68 (3H, m), 7.15 (1H, t, $J=8.1$ Hz), 7.98-8.08 (2H, m), 8.58-8.68 (2H, m).

15 **Example 33**

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (550 mg), methyl 3-(3-hydroxyphenyl)propionate (330 mg), tributylphosphine (700 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (880 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). 20 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was 25 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propionic acid (590 mg, yield 73%). The 30 crystals were recrystallized from isopropyl ether-hexane.

melting point: 88-89°C.

¹H-NMR (CDCl₃)δ: 1.41 (3H, t, J=7.0 Hz), 2.00-2.18 (2H, m), 2.54-2.76 (4H, m), 2.88-3.02 (2H, m), 4.00 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.0 Hz), 6.71-6.88 (3H, m), 7.14-7.24 (1H, m), 7.77-7.96 (2H, m), 8.17 (1H, s), 8.52-8.60 (1H, m).

Example 34

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (520 mg), methyl 2-(4-hydroxyphenoxy)-2-methylpropionate (430 mg), triphenylphosphine (580 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (980 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-(4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenoxy)propionic acid (330 mg, yield 38%). The crystals were recrystallized from isopropyl ether-hexane.

melting point: 106-107°C.

¹H-NMR (CDCl₃)δ: 1.55 (6H, s), 2.39 (3H, s), 4.94 (2H, s), 6.85-6.99 (4H, m), 7.95-8.07 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

Example 35

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (460 mg), tributylphosphine

(650 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (820 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propionic acid (540 mg, yield 67%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.37-1.48 (6H, m), 2.02-2.16 (2H, m), 2.56-2.69 (4H, m), 2.83-2.94 (2H, m), 3.93-4.06 (4H, m), 4.34 (2H, q, $J=7.2$ Hz), 6.34-6.47 (2H, m), 7.02 (1H, d, $J=8.4$ Hz), 7.76-7.94 (2H, m), 8.17 (1H, s), 8.50-8.58 (1H, m).

Example 36

To a mixture of 1-methyl-3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)-1H-pyrazole-5-carbaldehyde (2.00 g), ethyl diethylphosphonoacetate (1.35 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 240 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(1-methyl-3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-

1H-pyrazol-4-ylmethoxy)-1H-pyrazol-5-yl)propenoate (2.14 g, yield 80%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.

5 melting point: 173-174°C.

¹H-NMR (CDCl₃)δ: 1.33 (3H, t, J=7.2 Hz), 2.40 (3H, s), 3.83 (3H, s), 4.26 (2H, q, J=7.2 Hz), 5.11 (2H, s), 5.94 (1H, s), 6.27 (1H, d, J=15.9 Hz), 7.47 (1H, d, J=15.9 Hz), 7.94-8.04 (2H, m), 8.57 (1H, s), 8.60-8.65 (1H, m).

10 Example 37

A mixture of ethyl (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoate (600 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml)

15 was stirred at 60°C for 2 hours. 1N Hydrochloric acid (10 ml) was added and the mixture was extracted with ethyl acetate.

The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoic acid (520 mg, yield 93%). The crystals were recrystallized from acetone-hexane. melting point: 208-209°C.

¹H-NMR (CDCl₃)δ: 2.41 (3H, s), 3.85 (3H, s), 5.13 (2H, s), 6.00 (1H, s), 6.28 (1H, d, J=15.8 Hz), 7.57 (1H, d, J=15.8 Hz), 7.93-8.07 (2H, m), 8.58 (1H, s), 8.60-8.66 (1H, m).

Example 38

A mixture of ethyl (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoate (1.25 g), 5% palladium-carbon (600 mg) and tetrahydrofuran (30 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml)

was stirred at room temperature for 3 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propionic acid (1.13 g, yield 96%). The crystals were recrystallized from acetone-hexane. melting point: 154-
10 155°C.

1H -NMR ($CDCl_3$) δ : 2.39 (3H, s), 2.64-2.77 (2H, m), 2.81-2.94 (2H, m), 3.68 (3H, s), 5.07 (2H, s), 5.51 (1H, s), 7.94-8.07 (2H, m), 8.54 (1H, s), 8.60-8.65 (1H, m).

Example 39

To a mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (1.50 g), methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (830 mg), triphenylphosphine (1.40 g) and tetrahydrofuran (30 ml) was dropwise added a 40% solution (2.35 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazole-5-carboxylate (2.00 g, yield 90%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

1H -NMR ($CDCl_3$) δ : 1.36 (6H, d, $J=6.9$ Hz), 3.10-3.24 (1H, m), 3.87 (3H, s), 4.06 (3H, s), 5.15 (2H, s), 6.21 (1H, s), 7.94-8.10 (2H, m), 8.57 (1H, s), 8.61-8.66 (1H, m).

Example 40

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (3.95 g), methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (2.39 g),

triphenylphosphine (4.50 g) and tetrahydrofuran (50 ml) was dropwise added a 40% solution (7.60 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was 5 concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-methyl-3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy)-1H-pyrazole-5-carboxylate (4.90 g, yield 81%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131°C.
10
¹H-NMR (CDCl₃)δ: 2.40 (3H, s), 3.86 (3H, s), 4.05 (3H, s), 5.12 (2H, s), 6.20 (1H, s), 7.94-8.06 (2H, m), 8.57 (1H, s), 8.59-8.67 (1H, m).

15 **Example 41**

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (0.40 g), methyl 2-(3-hydroxyphenoxy)-2-methylpropionate (280 mg), tributylphosphine (500 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was 20 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was 25 washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenoxy]propionic acid (300 mg, yield 48%). The 30 crystals were recrystallized from ethyl acetate-hexane.

melting point: 99-100°C.

¹H-NMR (CDCl₃)δ: 1.00 (3H, t, J=7.0 Hz), 1.61 (6H, s), 1.60-1.83 (2H m), 1.98-2.10 (2H, m), 2.55-2.76 (4H, m), 3.98 (2H, t, J=6.2 Hz), 6.50-6.70 (3H, m), 7.11-7.24 (1H, m), 7.90-8.08 (2H, m), 8.27 (1H, s), 8.55-8.64 (1H, m).

Example 42

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (440 mg), tributylphosphine (650 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid (460 mg, yield 55%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 121-122°C.

¹H-NMR (CDCl₃)δ: 1.42 (3H, t, J=7.0 Hz), 1.96-2.18 (2H, m), 2.52-2.71 (4H, m), 2.88-3.00 (2H, m), 4.17-4.28 (2H, m), 4.35 (2H, q, J=7.0 Hz), 5.71 (1H, s), 7.27-7.50 (5H, m), 7.76-7.95 (2H, m), 8.17 (1H, s), 8.50-8.56 (1H, m).

Example 43

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (540 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (450 mg),

tributylphosphine (700 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (860 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-phenyl-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-5-yl]propionic acid (630 mg, yield 69%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 149-150°C.

1H -NMR ($CDCl_3$) δ : 1.00 (3H, t, $J=7.2$ Hz), 1.62-1.85 (2H, m), 1.98-2.18 (2H, m), 2.55-2.71 (6H, m), 2.88-3.02 (2H, m), 4.18-4.30 (2H, m), 5.71 (1H, s), 7.27-7.51 (5H, m), 7.89-8.06 (2H, m), 8.29 (1H, s), 8.55-8.62 (1H, m).

Example 44

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (550 mg), methyl 3-hydroxyphenylacetate (300 mg), tributylphosphine (740 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (890 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N

Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (630 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 106-107°C.

¹⁰ 1H -NMR ($CDCl_3$) δ : 1.00 (3H, t, $J=7.0$ Hz), 1.62-1.82 (2H m), 2.00-2.18 (2H, m), 2.55-2.74 (4H, m), 3.62 (2H, s), 4.03 (2H, t, $J=6.2$ Hz), 6.70-6.92 (3H, m), 7.17-7.32 (1H, m), 7.90-8.05 (2H, m), 8.30 (1H, s), 8.58-8.64 (1H, m).

Example 45

¹⁵ To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (320 mg), tributylphosphine (650 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, ²⁵ 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-methyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propionic acid (550 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: ³⁵ 80-81°C.

¹H-NMR (CDCl₃) δ: 1.00 (3H, t, J=7.4 Hz), 1.60–1.84 (2H, m), 1.95–2.14 (2H, m), 2.54–2.93 (8H, m), 3.66 (3H, s), 4.08–4.20 (2H, m), 5.48 (1H, s), 7.90–8.06 (2H, m), 8.28 (1H, s), 8.57–8.64 (1H, m).

5 **Example 46**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 4-hydroxyphenylacetate (300 mg), tributylphosphine (750 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (890 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate–hexane (1:4, volume ratio).
10 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
15 washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 75%). The
20 crystals were recrystallized from ethyl acetate–hexane.
25 melting point: 101–102°C.

¹H-NMR (CDCl₃) δ: 1.00 (3H, t, J=7.4 Hz), 1.62–1.84 (2H m), 2.01–2.19 (2H, m), 2.55–2.73 (4H, m), 3.60 (2H, s), 3.96–4.06 (2H, m), 6.82–6.92 (2H, m), 7.14–7.24 (2H, m), 7.90–8.06 (2H, m), 8.30 (1H, s), 8.57–8.64 (1H, m).

Example 47

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 2-hydroxyphenylacetate (300 mg), tributylphosphine (750 mg) and tetrahydrofuran (30 ml) was added 1,1'-

azodicarbonyldipiperidine (900 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (620 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 100-101°C.

Example 48

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (346 mg), tributylphosphine (790 μL) and tetrahydrofuran (53 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-

hexane to give 3-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1-methyl-1H-pyrazol-5-yl]propanoic acid (370 mg, yield 50%). melting point: 137-138°C.

5 Example 49

To a mixture of 4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (437 mg), tributylphosphine (761 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (594 mg, yield 72%): melting point: 137-138°C.

Example 50

To a mixture of 4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (333 mg), tributylphosphine (761 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-methyl-1H-pyrazol-5-yl]propanoic acid (366 mg, yield 50%). melting point: 113-114°C.

Example 51

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-hydroxyphenylacetate (279 mg), tributylphosphine (761 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:20, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 6 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from diisopropyl ether-hexane, [3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (165 mg, yield 23%). melting point: 114-115°C.

Example 52

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 2-hydroxyphenylacetate (279 mg), tributylphosphine (761 µL) and tetrahydrofuran (80 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [2-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (376 mg, yield 53%). melting point: 125-126°C.

Example 53

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 4-hydroxyphenylacetate (279 mg), tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (335 mg, yield 47%). melting point: 130-131°C.

Example 54

To a mixture of 4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (353 mg), tributylphosphine (761 μL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 2-[3-(4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)phenoxy]-2-methylpropanoic acid (258 mg, yield 33%). melting point: 81-82°C.

Example 55

To a mixture of 4-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), methyl 3-(4-hydroxyphenyl)propanoate (303 mg), tributylphosphine (761 μL) and tetrahydrofuran (76 ml) was added 1,1'-

azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]propanoic acid (231 mg, yield 32%). melting point: 144-145°C.

Example 56

To a mixture of 2-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)ethanol (300 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (285 mg), tributylphosphine (496 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (503 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (15 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(2-(3-ethoxy-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl)ethoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (372 mg, yield 72%). melting point: 155-156°C.

Example 57

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (300 mg), methyl 2-hydroxyphenylacetate (183 mg), tributylphosphine (496 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (502 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [2-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenyl]acetic acid (242 mg, yield 56%). melting point: 134-135°C.

Example 58

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (437 mg), tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[1-phenyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-5-yl]propanoic acid (505 mg, yield 61%). melting point: 123-124°C.

Example 59

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-hydroxyphenylacetate (508 mg), tributylphosphine (761 μ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3.5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (330 mg, yield 47%). melting point: 96-97°C.

Example 60

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 2-

hydroxyphenylacetate (279 mg), tributylphosphine (761 μ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [2-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (236 mg, yield 33%). melting point: 95-97°C.

Example 61

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (286 mg), tributylphosphine (761 μ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained

colorless crystals were recrystallized from ethyl acetate-hexane to give [1-methyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-4-yl]acetic acid (340 mg, yield 48%). melting point: 5 95-97°C.

Example 62

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (460 mg), methyl 3-hydroxyphenylacetate (507 mg), tributylphosphine (761 µL) and 10 tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a 15 fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was 20 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane 25 (1:2, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenyl]acetic acid (206 mg, yield 31%). melting point: 128-130°C.

30 Example 63

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-hydroxy-4-methoxyphenylacetate (899 mg), tributylphosphine (1.14 ml) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (1.16 g) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
10 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-methoxy-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (388 mg, yield 52%). melting
15 point: 147-148°C.

Example 64

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propanoate (350 mg), tributylphosphine (761 μ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was
25 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methyl-4-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]propanoic acid (323 mg, yield 43%). melting
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point: 105–107°C.

Example 65

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (480 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propanoate (351 mg), tributylphosphine (763 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (773 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methyl-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (147 mg, yield 20%).
melting point: 124–126°C.

Example 66

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (390 mg), tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature

overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [1-phenyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-4-yl]acetic acid (600 mg, yield 74%). melting point: 114-115°C.

Example 67

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (480 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (391 mg), tributylphosphine (763 μ L) and tetrahydrofuran (77 ml) was added 1,1'-azodicarbonyldipiperidine (773 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [1-phenyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (601 mg, yield 76%). melting point: 123-124°C.

Example 68

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (390 mg),

tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-phenyl-1H-pyrazol-4-yl]acetic acid (471 mg, yield 58%). melting point: 119-120°C.

Example 69

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (350 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propanoate (674 mg), tributylphosphine (799 µL) and tetrahydrofuran (53 ml) was added 1,1'-azodicarbonyldipiperidine (809 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(4-{3-

isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)-2-methoxyphenyl]propanoic acid (319 mg, yield 59%). melting point: 125-126°C.

Example 70

5 To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (333 mg), tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance,
15 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
20 solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[1-methyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-5-yl]propanoic acid (345 mg, yield 47%). melting
25 point: 122-123°C.

Example 71

To a mixture of 3-(3-(benzyloxy)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (247 mg),
30 tributylphosphine (394 µL) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (399 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane
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(1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the 5 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(3-(benzyloxy)-1-[5-(trifluoromethyl)- 10 2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1-phenyl-1H-pyrazol-5-yl]propanoic acid (378 mg, yield 81%). melting point: 159-161°C.

Example 72

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (339 mg), tributylphosphine (662 μ L) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The 20 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran 25 (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-1-phenyl-1H-pyrazol-4-yl]acetic acid (544 mg, yield 82%). melting point: 135-137°C.

Example 73

35 To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl)ethanol (400 mg), methyl 4-hydroxyphenylacetate (243 mg), tributylphosphine (662 μ L) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-(2-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)ethoxy)phenyl]acetic acid (123 mg, yield 21%). melting point: 142-143°C.

20 Example 74

To a mixture of 2-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)ethanol (400 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (335 mg), tributylphosphine (662 μ L) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained colorless crystals were 5 recrystallized from ethyl acetate-hexane to give 2-[3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenoxy]-2-methylpropanoic acid (169 mg, yield 26%). melting point: 89-90°C.

Example 75

10 To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (350 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propanoate (733 mg), tributylphosphine (868 µL) and tetrahydrofuran (58 ml) was added 1,1'-azodicarbonyldipiperidine (879 mg) at room temperature and the 15 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous 20 sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 days. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried 25 (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1.5, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-2-methoxyphenyl]propanoic acid (337 mg, yield 61%). 30 melting point: 147-148°C.

Example 76

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), ethyl 3-(4-

hydroxy-2-methylphenyl)propanoate (332 mg), tributylphosphine (662 μ L) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-2-methylphenyl]propanoic acid (210 mg, yield 34%). melting point: 117-119°C.

Example 77

A mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl methanesulfonate (500 mg), sodium hydride (60%, in oil, 74.0 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 30 minutes and a solution of ethyl 3-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]propanoate (350 mg) in N,N-dimethylformamide (2 ml) was added. After stirring overnight, water was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was

added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-fluorophenyl)-1-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoic acid (395 mg, yield 59%). melting point: 119-121°C.

Example 78

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (500 mg), sodium hydride (60%, in oil, 113 mg) and N,N-dimethylformamide (22 ml) was stirred at room temperature for 1 hour and 4-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butyl methanesulfonate (870 mg) was added. After stirring the resulting mixture overnight, 0.1N aqueous hydrochloric acid solution (100 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.39 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 1 hour and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give sodium 3-[3-ethoxy-1-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoate (657 mg, yield 59%). melting point:

250-251°C.

Example 79

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (470 mg), ethyl 4-hydroxy-3-methoxyphenylacetate (320 mg), tributylphosphine (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (760 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-4-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (550 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

Example 80

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (510 mg), methyl 3-hydroxy-4-methoxyphenylacetate (799 mg), tributylphosphine (1.01 ml) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and

ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-methoxy-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (451 mg, yield 58%). melting point: 124-126°C.

10 Example 81

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (560 mg), ethyl 3-(5-hydroxy-2-methoxyphenyl)propanoate (441 mg), tributylphosphine (892 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (903 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methoxy-5-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoic acid (407 mg, yield 46%). melting point: 104-106°C.

Example 82

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-

pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 3-(4-hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propionic acid (650 mg, yield 88%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 118-119°C.

Example 83

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 3-(2-hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (420 mg, yield 57%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

Example 84

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(3-hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (520 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 97-98°C.

Example 85

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (340 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
10 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-methoxyphenyl]propionic acid (530 mg, yield 67%). The crystals
15 were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

Example 86

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (510 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N
20 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl)propoxy)phenyl]propionic acid (520 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

Example 87

5 To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (510 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (290 mg), tributylphosphine (680 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (860 mg) at room
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,
15 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried
20 ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [1-methyl-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-4-yl]acetic acid (570 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point:
25 119-120°C.

Example 88

To a mixture of 4-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), methyl 4-hydroxyphenylacetate (270 mg), tributylphosphine (620 mg) and
30 tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (780 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
35 fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (410 mg, yield 58%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

Example 89

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (510 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (330 mg), tributylphosphine (630 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (790 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)phenyl]propionic acid (510 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 91-92°C.

35 Example 90

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (190 mg), methyl 2-fluoro-5-hydroxyphenylacetate (110 mg), tributylphosphine (250 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (310 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-fluoro-5-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (220 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 111-112°C.

Example 91

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (390 mg), methyl 4-fluoro-3-hydroxyphenylacetate (230 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [4-fluoro-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (220 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 88-89°C.

Example 92

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 3-(3-hydroxy-5-methoxyphenyl)propionate (380 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and ethanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-5-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propionic acid (380 mg, yield 48%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 98-99°C.

Example 93

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 3-(3-hydroxy-4-methoxyphenyl)propionate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (35 ml) was added 1,1'-

azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-methoxy-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenylpropionic acid (280 mg, yield 70%). melting point: 147-148°C.

Example 94

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (650 mg), methyl 4-hydroxy-2-methylphenylacetate (390 mg), tributylphosphine (840 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (1050 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-methyl-4-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl)propoxy)phenyl]acetic acid (590 mg, yield 62%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

Example 95

5 To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (470 mg), methyl 4-hydroxy-2-methoxyphenylacetate (300 mg), tributylphosphine (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (760 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium
15 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried
20 ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-methoxy-4-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
25 yl)propoxy)phenyl]acetic acid (580 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane.
melting point: 135-136°C.

Example 96

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (470 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (350 mg), tributylphosphine
30 (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (760 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
35 fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted 5 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
10 yl}propoxy)phenyl]propionic acid (590 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 126-127°C.

Example 97

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (580 mg), methyl (5-hydroxy-2-methoxyphenyl)acetate (400 mg), tributylphosphine (924 μ L) and tetrahydrofuran (90 ml) was added 1,1'-azodicarbonyldipiperidine (936 mg) at room temperature and the mixture was stirred for 3 days. The reaction solution was 20 concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and 25 ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained pale-yellow crystals 30 were recrystallized from ethyl acetate-hexane to give [2-methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (483 mg, yield 55%) as colorless crystals. melting point: 135-136°C.

Example 98

35 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(4-hydroxy-2-ethoxyphenyl)propanoate (395 mg), tributylphosphine (797 μ L) and tetrahydrofuran (80 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (442 mg, yield 55%) as colorless crystals. melting point: 119-120°C.

20 **Example 99**

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-(4-hydroxy-2-ethoxyphenyl)propanoate (260 mg), tributylphosphine (480 μ L) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and

concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenoxy]propanoic acid (373 mg, yield 60%) as 5 colorless crystals. melting point: 135-136°C.

Example 100

A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (300 mg), sodium hydride (60%, in oil, 63.6 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 30 minutes and iodocyclopentane (184 µL) was added. After stirring overnight, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. A mixture of the obtained residue, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).
A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (645 µL), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (25 ml) was added calcium chloride (69.0 mg) dissolved in a small amount of water, and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-{3-[3-(1-cyclopentyl-3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (256 mg, yield 74%) as amorphous.
¹H-NMR (DMSO-d₆) δ: 1.25 (3H, t, J = 6.9 Hz), 1.41 (6H, s),

1.52 - 1.61 (2H, m), 1.67 - 2.00 (8H, m), 2.32 - 2.39 (2H, m), 3.83 - 3.90 (2H, m), 4.09 (2H, q, $J = 6.9$ Hz), 4.34 - 4.45 (1H, m), 6.34 - 6.44 (3H, m), 6.96 - 7.04 (1H, m), 7.35 (1H, s).

5 Example 101

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (420 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (419 mg), tributylphosphine (847 μ L) and tetrahydrofuran (34 ml) was added 1,1'-azodicarbonyldipiperidine (858 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).
10 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
15 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 2-(3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy)phenoxy)-2-methylpropanoic acid (291 mg, yield 40%). melting point: 99-
20 101°C.
25

Example 102

A mixture of ethyl 2-{3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenoxy}-2-methylpropanoate (740 mg), sodium hydride (60%, in oil, 90.8 mg) and N,N-dimethylformamide (20 ml) was
30 stirred at room temperature for 30 minutes and 2-chloro-5-(trifluoromethyl)pyridine (412 mg) was added. After stirring the reaction mixture overnight, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with
35 saturated aqueous sodium chloride solution, dried ($MgSO_4$) and

concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 2.5 days. 5 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried 10 ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (893 μL), tetrahydrofuran (25 ml) and 15 ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (25 ml) was added calcium chloride (90.8 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were 20 collected by filtration to give calcium 2-[3-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenoxy]-2-methylpropanoate (394 mg, yield 39%) as amorphous.

1H -NMR (DMSO-d₆) δ : 1.36 (3H, t, J = 7.2 Hz), 1.40 (6H, s), 25 1.62 – 1.78 (4H, m), 2.36 – 2.46 (2H, m), 3.85 – 3.94 (2H, m), 4.31 (2H, q, J = 7.2 Hz), 6.34 – 6.44 (3H, m), 6.95 – 7.04 (1H, m), 7.79 (1H, d, J = 8.7 Hz), 8.20 – 8.27 (1H, m), 8.32 (1H, s), 8.69 – 8.74 (1H, m).

Example 103

30 To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (346 mg), tributylphosphine (603 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the 35 mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-(3-[3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy]-1-phenyl-1H-pyrazol-5-yl)propanoic acid (483 mg, yield 87%). melting point: 156-157°C.

15 Example 104

A mixture of ethyl 3-(3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]-1-phenyl-1H-pyrazol-5-yl)propanoate (900 mg), sodium hydride (60%, in oil, 101 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 30 minutes. 2-Chloro-5-(trifluoromethyl)pyridine (459 mg) was added. After stirring the obtained mixture overnight, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. A mixture of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give 3-[3-(4-{3-

ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (640 mg, yield 56%) as colorless crystals. melting point: 138-139°C.

Example 105

5 To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (512 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (401 mg), tributylphosphine (812 μ L) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (823 mg) at room
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,
15 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
20 solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (995 μ L),
25 tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (110 mg) dissolved in water (5 ml) and the mixture was stirred overnight at room temperature. The resulting white
30 precipitates were collected by filtration to give calcium 2-[3-{3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy}phenoxy]-2-methylpropanoate (440 mg, yield 53%) as amorphous.

1H -NMR (DMSO-d₆) δ : 1.28 - 1.48 (3H, m), 1.41 (6H, s), 1.87 -
35 2.08 (2H, m), 2.41 - 2.56 (2H, m), 3.86 - 4.00 (2H, m), 4.20 -

4.39 (2H, m), 6.31 – 6.52 (3H, m), 6.93 – 7.10 (1H, m), 7.69 – 7.96 (4H, m), 8.38 (1H, s).

Example 106

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl 3-hydroxyphenylacetate (402 mg), tributylphosphine (603 µL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless oil was recrystallized from diisopropyl ether-hexane to give (3-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (247 mg, yield 53%) as colorless crystals. melting point: 66–67°C.

Example 107

A mixture of methyl 3-{2-ethoxy-4-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}propanoate (860 mg), sodium hydride (60%, in oil, 106 mg) and N,N-dimethylformamide (25 ml) was stirred at room temperature for 30 minutes and 2-chloro-5-(trifluoromethyl)pyridine (479 mg) was added. After stirring overnight, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N

Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(4-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)phenyl]propanoic acid (718 mg, yield 63%) as colorless crystals. melting point: 101-102°C.

Example 108

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (298 mg), tributylphosphine (603 μ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-(2-ethoxy-4-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenyl)propanoic acid (323 mg, yield 61%). melting point: 110-111°C.

Example 109

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), ethyl 3-(4-hydroxy-3-

methoxyphenyl)propanoate (298 mg), tributylphosphine (603 μ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-(4-(3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)propanoic acid (416 mg, yield 81%). melting point: 92-93°C.

Example 110

A mixture of ethyl 3-(3-ethoxy-1-[4-(3-ethoxy-1H-pyrazol-4-yl)butyl]-1H-pyrazol-4-yl)propanoate (680 mg), sodium hydride (60%, in oil, 86.4 mg) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 30 minutes and 2-chloro-5-(trifluoromethyl)pyridine (391 mg) was added. After stirring the obtained mixture for 7 hours, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue

was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (134 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 3-[3-ethoxy-1-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoate (654 mg, yield 71%) as amorphous.

¹H-NMR (DMSO-d₆) δ: 1.22 (3H, t, J = 6.9 Hz), 1.36 (3H, t, J = 6.9 Hz), 1.40 – 1.54 (2H, m), 1.66 – 1.78 (2H, m), 2.26 – 2.44 (4H, m), 2.46 – 2.58 (2H, m), 3.69 – 3.78 (2H, m), 4.11 (2H, q, J = 6.9 Hz), 4.27 (2H, q, J = 6.9 Hz), 6.93 (1H, s), 7.71 (1H, d, J = 8.4 Hz), 7.79 – 7.85 (1H, m), 8.05 (1H, s), 8.44 – 8.49 (1H, m).

20 Example 111

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (157 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (130 mg), tributylphosphine (249 μL) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (252 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride

solution, dried ($MgSO_4$) and concentrated. The obtained colorless oil was recrystallized from ethyl acetate-hexane to give 3-[3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)propoxy]-1-phenyl-1H-pyrazol-5-yl]propanoic acid (99.5 mg, yield 38%) as colorless crystals. melting point: 126-127°C.

Example 112

A mixture of ethyl 3-[2-(benzyloxy)-4-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]phenylpropanoate (250 mg), 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-(benzyloxy)-4-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]phenylpropanoic acid (237 mg, yield 99%) as colorless crystals. melting point: 128-130°C.

Example 113

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (422 mg), tributylphosphine (633 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(3-{3-
5 ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-
yl}propoxy)phenyl]acetic acid (424 mg, yield 74%). melting
point: 108-109°C.

Example 114

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (314 mg), tributylphosphine (633 μ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-
25 yl}propoxy)phenyl]propanoic acid (420 mg, yield 65%) as colorless crystals. melting point: 131-132°C.

Example 115

30 To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (314 mg), tributylphosphine (633 μ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The

reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,
5 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
10 solution, dried ($MgSO_4$) and concentrated. The obtained colorless oil was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (423 mg, yield 68%) as colorless crystals. melting point: 125-126°C.

15 **Example 116**

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-hydroxyphenyl]propanoate (300 mg), isopropanol (49.5 μL), tributylphosphine (294 μL) and tetrahydrofuran (15 ml) was
20 added 1,1'-azodicarbonyldipiperidine (298 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,
25 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
30 solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-isopropoxypyhenyl]propanoic acid (76.0
35 mg, yield 25%) as colorless crystals. melting point: 104-

105°C.

Example 117

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-hydroxyphenyl]propanoate (400 mg), propanol (119 µL), tributylphosphine (393 µL) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (399 mg) at room temperature and the mixture was stirred for 2.5 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-propoxyphenyl]propanoic acid (259 mg, yield 63%) as colorless crystals. melting point: 126-127°C.

Example 118

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-hydroxyphenyl]propanoate (470 mg), butanol (170 µL), tributylphosphine (461 µL) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (467 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room

temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-butoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (235 mg, yield 47%) as colorless crystals. melting point: 123-124°C.

Example 119

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (463 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (250 mg), tributylphosphine (728 μL) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (764 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-5-yl]acetic acid (255 mg, yield 39%) as colorless crystals.

melting point: 151-152°C.

Example 120

To a mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (250 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (180 mg), triphenylphosphine (280 mg) and tetrahydrofuran (10 ml) was

dropwise added a 40% solution (460 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-((3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (210 mg, yield 53%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 153-154°C.

Example 121

To a mixture of (3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (410 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propionate (300 mg), triphenylphosphine (450 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (750 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were

collected by filtration to give 3-[2-methyl-4-((3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (460 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane.

⁵ melting point: 129-130°C.

Example 122

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (220 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (180 mg),

¹⁰ triphenylphosphine (260 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (450 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column ¹⁵ chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N

²⁰ hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-((3-methyl-1-[5-

²⁵ (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (220 mg, yield 59%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 158-159°C.

Example 123

³⁰ To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (380 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propionate (300 mg), triphenylphosphine (450 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (450 mg) of diethyl azodicarboxylate in toluene at ³⁵ room temperature and the mixture was stirred overnight. The

reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,
5 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried
10 ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methyl-4-((3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
yl)methoxy)phenyl]propionic acid (380 mg, yield 63%). The crystals were recrystallized from ethyl acetate-hexane.
15 melting point: 144-145°C.

Example 124

To a mixture of 3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (200 mg), tributylphosphine (480 mg) and
20 tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
25 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted
30 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (520 mg,
35 yield 94%). The crystals were recrystallized from ethyl

acetate-hexane. melting point: 132-133°C.

Example 125

To a mixture of 3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (420 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (320 mg), tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-phenyl-3-(3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-5-yl]propionic acid (640 mg, yield 94%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 175-176°C.

Example 126

To a mixture of 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (420 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (330 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (510 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 129-130°C.

Example 127

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (240 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (550 mg, yield 93%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

Example 128

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (390 mg),

tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-1-phenyl-1H-pyrazol-5-yl]propionic acid (700 mg, yield 95%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

Example 129

To a mixture of 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (420 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (330 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected

by filtration to give 3-[3-methoxy-4-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (510 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane.

⁵ melting point: 136-137°C.

Example 130

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropionate (340 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]propionic acid (520 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 107-108°C.

Example 131

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (460 mg), ethyl 3-hydroxy-4-methoxyphenylacetate (310 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-4-methoxyphenyl]acetic acid (560 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

Example 132

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 2-hydroxy-5-methoxyphenylacetate (250 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-5-methoxyphenyl]acetic acid (560 mg, yield 92%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.

Example 133

To a mixture of 3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropionate (260 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)phenoxy]propionic acid (540 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 141-142°C.

Example 134

To a mixture of 3-(3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 2-hydroxyphenylacetate (240 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted

with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-phenyl-1-[5-(trifluoromethyl)-
5 2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (510 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 133-134°C.

Example 135

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-
10 pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (220 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The
15 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran
20 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were
25 collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (440 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 115-116°C.

Example 136

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (300 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was
35 added 1,1'-azodicarbonyldipiperidine (650 mg) at room

temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-4-yl]acetic acid (580 mg, yield 89%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 117-118°C.

Example 137

To a mixture of methyl {2-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}acetate (550 mg), 2-chloro-5-(trifluoromethyl)pyridine (300 mg) and N,N-dimethylformamide (5 ml) was added sodium hydride (60%, in oil, 70 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were

collected by filtration to give [2-(4-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)butoxy)phenyl]acetic acid (100 mg, yield 13%). The crystals were recrystallized from ethyl acetate-hexane. melting point:
5 109-110°C.

Example 138

A mixture of methyl {2-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}acetate (1.52 g), 4-(trifluoromethyl)phenylboric acid (1.74 g), copper(II) acetate (1.25 g), pyridine (0.67 ml) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 3 days. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (10 ml), tetrahydrofuran (10 ml) and methanol (10 ml) was stirred at room temperature for 1 hour.
1N Hydrochloric acid (10 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml) and methanol (5 ml) was stirred at room temperature for 30 minutes. After concentration, water (15 ml) was added. A solution of calcium chloride (350 mg) in water (5 ml) was slowly added while stirring the mixture at room temperature.
25 The obtained colorless amorphous was removed by filtration to give calcium [2-(4-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)butoxy)phenyl]acetate (830 mg, yield 38%).

Example 139

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 5-

chloro-2-hydroxyphenylacetate (260 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was 5 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol 10 (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected 15 by filtration to give [5-chloro-2-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (580 mg, yield 94%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131°C.

20 **Example 140**

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(2-hydroxy-5-methoxyphenyl)propionate (290 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was 25 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol 30 (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and 35

concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]propionic acid (470 mg, yield 75%). The crystals
5 were recrystallized from ethyl acetate-hexane. melting point: 104-105°C.

Example 141

To a mixture of 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 2-hydroxyphenylacetate (240 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N
15 hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (410 mg,
20 yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 128-129°C.
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Example 142

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (300 mg), methyl 2-hydroxy-4-methoxyphenylacetate (190 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
35 concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (310 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 147-148°C.

Example 143

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), ethyl 3-(2-hydroxy-4-methoxyphenyl)propionate (220 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]propionic acid (340 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 115-116°C.

Example 144

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (300 mg), methyl 3-(2-hydroxyphenyl)propionate (180 mg), tributylphosphine (400 mg)
5 and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
10 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted
15 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
20 yl}propoxy)phenyl]propionic acid (360 mg, yield 82%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 93-94°C.

Example 145

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (300 mg), ethyl 3-(2-hydroxy-3-methoxyphenyl)propionate (220 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
25 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol
30 (5 ml) was stirred at room temperature for 5 hours and 1N
35

hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propionic acid (360 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

Example 146

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (200 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (190 mg, yield 42%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.

Example 147

To a mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (300 mg), methyl 3-hydroxyphenylacetate (190 mg), tributylphosphine (430 mg) and tetrahydrofuran (30 ml) was added 1,1'-

azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (340 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 77-78°C.

Example 148

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), ethyl 3-(2-hydroxy-6-methoxyphenyl)propionate (220 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-6-

methoxyphenyl]propionic acid (170 mg, yield 36%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 110-111°C.

Example 149

5 To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (300 mg), methyl 3-hydroxyphenylacetate (250 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium
15 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and
20 concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (330 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

25 **Example 150**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (310 mg), tributylphosphine (530 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
35 A mixture of the obtained oily substance, 1N aqueous sodium

hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-3-methoxyphenyl]propanoic acid (440 mg, yield 69%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 131-132°C.

Example 151

A mixture of methyl 3-[2-ethoxy-4-(3-(3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoate (500 mg), 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and concentrated. 1N Hydrochloric acid (3 ml) was added and the obtained colorless crystals were collected by filtration, washed with water and acetonitrile and dried to give 3-[2-ethoxy-4-(3-(3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoic acid (470 mg, yield 97%). melting point: 192-194°C.

Example 152

To a mixture of methyl 3-[2-ethoxy-4-(3-(3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoate (600 mg), methyl iodide (0.11 ml) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 58 mg) at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl

acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-methoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (350 mg, yield 58%). The crystals were recrystallized from isopropyl ether. melting point: 145-146°C.

Example 153

To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (600 mg), 1-iodopropane (0.14 mL) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 58 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-propoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (380 mg, yield 60%). The crystals were recrystallized from

isopropyl ether. melting point: 112-113°C.

Example 154

To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (600 mg), 2-propanol (0.15 ml), triphenylphosphine (480 mg) and tetrahydrofuran (10 ml) was added diisopropyl azodicarboxylate (370 mg) at room temperature and the mixture was stirred for 3 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-isopropoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (520 mg, yield 82%). The crystals were recrystallized from isopropyl ether. melting point: 128-129°C.

Example 155

To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (600 mg), 1-iodobutane (0.17 ml) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 58 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with

ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml)
5 was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-butoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-
10 pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoic acid (320 mg, yield 49%). The crystals were recrystallized from isopropyl ether. melting point: 102-103°C.

Example 156

A mixture of methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoate (600 mg), 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with
20 ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-
25 ethoxyphenyl]propanoic acid (380 mg, yield 65%). The crystals were recrystallized from isopropyl ether. melting point: 106-107°C.

Example 157

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(4-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
35 concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[4-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenylpropanoic acid (250 mg, yield 54%). The crystals were recrystallized from hexane. melting point: 84-85°C.

Example 158

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(4-hydroxyphenyl)-2-methylpropanoate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated to give 2-[4-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl-2-methylpropanoic acid (410 mg, yield 84%) as a yellow oily substance.

¹H-NMR ($CDCl_3$) δ : 1.40 (3H, t, J=7.1 Hz), 1.58 (6H, s), 2.08 (2H, quintet, J=7.3 Hz), 2.60 (2H, t, J=7.4 Hz), 3.99 (2H, t, J=6.2 Hz), 4.34 (2H, q, J=7.1 Hz), 6.84-6.89 (2H, m), 7.28-

7.33 (2H, m), 7.81 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=8.7, 2.3 Hz), 8.19 (1H, s), 8.54-8.56 (1H, m).

Example 159

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 2-(3-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoic acid (320 mg, yield 42%). The crystals were recrystallized from hexane. melting point: 82-83°C.

Example 160

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 2-(3-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium

hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 5 saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]-2-methylpropanoic acid (420 mg, yield 87%). The crystals were 10 recrystallized from hexane. melting point: 131-132°C.

Example 161

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), 1N aqueous sodium hydroxide 15 solution (3 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and 20 concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoic acid (330 mg, yield 75%). The crystals were recrystallized from isopropyl ether. melting point: 124-25 125°C.

Example 162

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), iodoethane (0.3 ml) and N,N-dimethylformamide (8 ml) was 30 stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue 35 was subjected to silica gel column chromatography, and

colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-ethoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (370 mg, yield 75%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 114-115°C.

Example 163

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), 1-iodopropane (0.2 ml) and N,N-dimethylformamide (8 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-propoxyphenyl]propanoic acid (440 mg, yield 86%). The crystals

were recrystallized from isopropyl ether-hexane. melting point: 106-107°C.

Example 164

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (200 mg), 2-propanol (0.11 ml), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (500 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 15 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-isopropoxyphenyl]propanoic acid (320 mg, yield 62%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 93-94°C.

Example 165

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), 1-iodobutane (0.3 ml) and N,N-dimethylformamide (8 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a

fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours.

5 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-butoxy-4-(3-{3-ethoxy-1-
10 [5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
yl}propoxy)phenyl]propanoic acid (450 mg, yield 86%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 92-93°C.

Example 166

15 A mixture of ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
yl}propoxy)phenyl]propanoate (665 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N
20 Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-benzyloxy-4-(3-{3-ethoxy-
25 1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
yl}propoxy)phenyl]propanoic acid (460 mg, yield 71%). The crystals were recrystallized from isopropyl ether. melting point: 115-116°C.

Example 167

30 To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-5-methoxyphenyl)propanoate (380 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the
35 mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[5-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (430 mg, yield 55%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 99-100°C.

Example 168

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-hydroxy-5-methoxyphenylacetate (345 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [5-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (370 mg, yield 49%). The crystals

were recrystallized from isopropyl ether. melting point: 125-126°C.

Example 169

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl 3-hydroxy-5-methoxyphenylacetate (345 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (410 mg, yield 54%). The crystals were recrystallized from isopropyl ether. melting point: 139-140°C.

Example 170

To a mixture of 3-(3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (9.04 g), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (6.42 g), triphenylphosphine (7.51 g) and tetrahydrofuran (150 ml) was added diisopropyl azodicarboxylate (5.79 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio), methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-

ethoxyphenyl]propanoate (13.03 g, yield 94%) as a pale-yellow oily substance.

¹H-NMR (CDCl₃) δ : 1.39 (3H, t, J=7.0 Hz), 2.08 (2H, quintet, J=7.2 Hz), 2.55-2.66 (4H, m), 2.86 (2H, t, J=7.7 Hz), 3.65 (3H, s), 3.93-4.00 (4H, m), 5.35 (2H, s), 6.35 (1H, dd, J=8.3, 2.4 Hz), 6.40 (1H, d, J=2.4 Hz), 7.00 (1H, d, J=8.3 Hz), 7.31-7.49 (5H, m), 7.84 (1H, d, J=8.8 Hz), 7.91-7.95 (1H, m), 8.22 (1H, s), 8.55-8.57 (1H, m).

Example 171

A mixture of methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoate (12.67 g), 5% palladium-carbon (1.3 g) and ethanol (150 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate as colorless crystals. melting point: 147-148°C.

Example 172

To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (3.00 g), ethyl 3-(3-benzyloxy-4-hydroxyphenyl)propanoate (2.90 g), tributylphosphine (3.84 g) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (4.80 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (4.14 g, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

¹H-NMR (CDCl₃) δ : 1.22 (3H, t, J=7.1 Hz), 1.40 (3H, t, J=7.1 Hz), 2.13 (2H, quintet, J=6.9 Hz), 2.57 (2H, t, J=7.8 Hz), 2.64 (2H, t, J=7.4 Hz), 2.86 (2H, t, J=7.8 Hz), 4.07 (2H, t, J=6.3 Hz), 4.11 (2H, q, J=7.1 Hz), 4.35 (2H, q, J=7.1 Hz),

5.11 (2H, s), 6.68 (1H, dd, J=8.2, 1.8 Hz), 6.76 (1H, d, J=2.0 Hz), 6.84 (1H, d, J=8.1 Hz), 7.27-7.47 (5H, m), 7.80 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=8.7, 2.3 Hz), 8.19 (1H, s), 8.53-8.55 (1H, m).

5 **Example 173**

A mixture of ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (4.14 g), 5% palladium-carbon (0.4 g), tetrahydrofuran (25 ml) and ethanol (25 ml) was
10 stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-
15 hydroxyphenyl]propanoate (3.25 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:20, volume ratio). melting point: 92-93°C.

Example 174

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (2.69 g), ethyl 3-[2-(benzyloxy)-4-hydroxyphenyl]propanoate (2.56 g), tributylphosphine (4.24 ml) and tetrahydrofuran (180 ml) was added 1,1'-azodicarbonyldipiperidine (4.29 g) at room temperature and the mixture was stirred for 3 days. The
25 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (2.79 g, yield 55%) was obtained as a white solid from a fraction
30 eluted with ethyl acetate-hexane (1:6, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane, colorless crystal. melting point: 80-81°C.

Example 175

A mixture of ethyl 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-

yl)propoxy)phenyl]propanoate (2.44 g), 5% palladium-carbon (1.00 g), tetrahydrofuran (25 ml) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the
5 filtrate was concentrated to give ethyl 3-[4-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-2-hydroxyphenyl]propanoate (1.63 g, yield 79%) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.23 (3H, t, J = 6.9 Hz), 1.41 (3H, t, J =
10 6.9 Hz), 2.01 – 2.12 (2H, m), 2.54 – 2.62 (2H, m), 2.64 – 2.71 (2H, m), 2.77 – 2.84 (2H, m), 3.92 – 3.98 (2H, m), 4.14 (2H, q, J = 6.9 Hz), 4.34 (2H, q, J = 6.9 Hz), 6.40 – 6.48 (2H, m), 6.94 (1H, d, J = 8.1 Hz), 7.50 (1H, s), 7.80 (1H, d, J = 8.7 Hz), 7.86 – 7.92 (1H, m), 8.17 (1H, s), 8.52 – 8.54 (1H, m).

15 **Example 176**

To a mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxyphenyl)acetate (300 mg), tributylphosphine (570 mg) and tetrahydrofuran (30 ml) was added 1,1'-
20 azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to
25 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for
30 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 3-{3-isopropyl-1-[5-
35 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl)methoxyphenylacetic acid (380 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

Example 177

5 To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (6-hydroxy-2-methoxyphenyl)acetate (260 mg), tributylphosphine (540 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
15 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture
20 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [6-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-2-
25 methoxyphenyl]acetic acid (490 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 150-151°C.

Example 178

To a mixture of {3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxyphenyl)acetate (350 mg), tributylphosphine (570 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
35 concentrated and isopropyl ether (20 ml) was added to the

residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (360 mg, yield 61%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 92-93°C.

Example 179

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (2-hydroxyphenyl)acetate (210 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (440 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

5 Example 180

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (430 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)-3-methoxyphenyl]acetic acid (550 mg, yield 85%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145°C.

Example 181

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was

concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

Example 182

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (230 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-(3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (430 mg, yield 76%). The crystals were recrystallized
5 from ethyl acetate-hexane. melting point: 114-115°C.

Example 183

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (3-hydroxy-4-methoxyphenyl)acetate (260 mg), tributylphosphine
10 (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and
15 the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran
20 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were
25 collected by filtration to give [3-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-4-methoxyphenyl]acetic acid (590 mg, yield 97%). The crystals were recrystallized from ethyl acetate-hexane. melting point:
122-123°C.

30 **Example 184**

To a mixture of 3-(3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (450 mg), methyl (2-hydroxyphenyl)acetate (250 mg), tributylphosphine
35 (590 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to 5 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 10 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[4- 15 (trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy]phenylacetic acid (560 mg, yield 87%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 89-90°C.

Example 185

To a mixture of 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (330 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The 25 reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl 30 acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The 35 ethyl acetate layer was washed with saturated aqueous sodium

chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (730 mg, yield 96%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

Example 186

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (2-fluoro-3-hydroxyphenyl)acetate (240 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (620 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-2-fluorophenyl]acetic acid (430 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

Example 187

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (380 mg), methyl (3-hydroxyphenyl)acetate (200 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-

azodicarbonyldipiperidine (610 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and
5 the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran
10 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were
15 collected by filtration to give [3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy]phenyl]acetic acid (480 mg, yield 89%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 129-130°C.

20 **Example 188**

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (430 mg), methyl (2-hydroxyphenyl)acetate (230 mg), tributylphosphine (530 mg) and tetrahydrofuran (30 ml) was added 1,1'-
25 azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to
30 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for
35 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture

was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy]phenyl]acetic acid (310 mg, yield 51%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

Example 189

To a mixture of 3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (300 mg), tributylphosphine (470 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (590 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid (190 mg, yield 30%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 182-183°C.

Example 190

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxy-

4-methoxyphenyl)acetate (250 mg), tributylphosphine (530 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (660 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
5 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane
10 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was
15 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-((3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy-4-methoxy)phenyl]acetic acid (240 mg, yield 40%). The crystals
20 were recrystallized from ethyl acetate-hexane. melting point:
145-146°C.

Example 191

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl 3-(3-hydroxyphenyl)propionate (230 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) To a mixture of was added 1,1'-azodicarbonyldipiperidine (660 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,
35 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran

(5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ⁵ ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxyphenyl)propionic acid (300 mg, yield 52%). The crystals were recrystallized from ethyl acetate-hexane.
¹⁰ melting point: 94-95°C.

Example 192

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (250 mg), ¹⁵ tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed ²⁰ by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), ²⁵ tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy-1-methyl-1H-pyrazol-5-yl)propionic acid (380 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 162-163°C.

³⁵ **Example 193**

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propionate (250 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy-1-methyl-1H-pyrazol-4-yl)propionic acid (410 mg, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

Example 194

To a mixture of 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (270 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran

(4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazole-2-yl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (130 mg, yield 22%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145.

Example 195

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 4-(3-hydroxyphenyl)butanoate (260 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxyphenyl)butanoic acid (390 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 128-129°C.

35 Example 196

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine (470 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (590 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenylacetic acid (290 mg, yield 50%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

Example 197

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (250 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane

(1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture 5 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-
10 methoxyphenyl]acetic acid (420 mg, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

Example 198

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (210 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was 20 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was 30 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (420 mg, yield 75%). The 35 crystals were recrystallized from ethyl acetate-hexane.

melting point: 106-107°C.

Example 199

To a mixture of 3-(3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (350 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (190 mg), tributylphosphine (450 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-(3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (420 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

Example 200

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (340 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to

silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [4-ethoxy-3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (580 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 116-117°C.

15 Example 201

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (250 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (580 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-

ethoxyphenyl]acetic acid (510 mg, yield 85%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

Example 202

5 To a mixture of 3-(3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (260 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
15 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture
20 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-(3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-4-
25 ethoxyphenyl]acetic acid (510 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

Example 203

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (5-hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
35 concentrated and isopropyl ether (20 ml) was added to the

residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]acetic acid (530 mg, yield 87%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 109-110°C.

Example 204

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (270 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were

collected by filtration to give [4-ethoxy-3-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (540 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane.

5 melting point: 124-125°C.

Example 205

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-4-methoxyphenyl)acetate (260 mg), tributylphosphine 10 (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and 15 the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran 20 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were 25 collected by filtration to give [2-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-4-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

30 Example 206

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-5-methoxyphenyl)acetate (270 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the 35

mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to 5 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 10 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-} 15 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

Example 207

20 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the 25 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture 30 was extracted with ethyl acetate. The ethyl acetate layer was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture 35 was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-fluoro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (560 mg, yield 94%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 140-141°C.

Example 208

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (6-hydroxy-2-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-6-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 183-184°C.

Example 209

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 5-hydroxy-2-methoxyphenylacetate (260 mg), tributylphosphine

(550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-methoxyphenyl]acetic acid (510 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 127-128°C.

Example 210

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (220 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (580 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for

5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were 5 collected by filtration to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-3-fluorophenyl]acetic acid (520 mg, yield 91%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 149-150°C.

10 **Example 211**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to 20 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 25 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-fluoro-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (510 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

Example 212

35 To a mixture of 3-{3-(1-ethylpropyl)-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (510 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 100-101°C.

Example 213

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (220 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained

oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The
5 ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid
10 (430 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

Example 214

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400
15 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (220 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml)
20 was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained
25 oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium
30 chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-fluorophenyl]acetic acid (390 mg, yield 60%). The crystals were recrystallized from
35 ethyl acetate-hexane. melting point: 102-103°C.

Example 215

To a mixture of 3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxyphenyl) acetate (200 mg),
5 tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed
10 by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml),
15 tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The
20 obtained colorless crystals were collected by filtration to give [2-(3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (370 mg, yield 66%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 65-66°C.

Example 216

To a mixture of 3-(3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl) acetate (250 mg), tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was
30 added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue
35 was subjected to silica gel column chromatography, and a

colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (510 mg, yield 85%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 117-118°C.

15 Example 217

To a mixture of 3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (300 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-

isopropyl-1H-pyrazol-4-yl)propoxy}-3-methoxyphenyl]acetic acid (610 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

Example 218

5 To a mixture of 3-[1-(5-bromo-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine (630 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (790 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
15 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture
20 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridyl)-
3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic
25 acid (720 mg, yield 95%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 152-153°C.

Example 219

To a mixture of 3-(3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (230 mg), tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml)
35 was added to the residue. The insoluble material was removed

by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methyl-2-(3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (380 mg, yield 66%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

Example 220

To a mixture of 3-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The

obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (480 mg, yield 81%). The 5 crystals were recrystallized from ethyl acetate-hexane. melting point: 107-108°C.

Example 221

To a mixture of 3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 10 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (250 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) 15 was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained 20 oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium 25 chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethoxy-2-(3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (540 mg, yield 89%). The crystals were recrystallized from ethyl 30 acetate-hexane. melting point: 83-84°C.

Example 222

To a mixture of 3-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (210 mg), 35 tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was

added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methyl-2-(3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]phenyl]acetic acid (360 mg, yield 63%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 147-148°C.

20 Example 223

To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (670 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (430 mg), tributylphosphine (910 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (1.15 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (40 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture

was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-
5 3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (760 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 85-86°C.

Example 224

10 To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (300 mg), tributylphosphine (660 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (820 mg) at room temperature and the
15 mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
20 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture
25 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-
3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl)acetic acid (280 mg, yield 46%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 106-107°C.

Example 225

To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (3-

ethoxy-2-hydroxyphenyl)acetate (350 mg), tributylphosphine (660 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (820 mg) at room temperature and the mixture was stirred overnight. The reaction solution was
5 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane
10 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
15 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-
3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-
ethoxyphenyl)acetic acid (590 mg, yield 75%). The crystals
20 were recrystallized from ethyl acetate-hexane. melting point:
92-93°C.

Example 226

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (3-
25 ethyl-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble
30 material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio), methyl [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-
35 1H-pyrazol-4-yl}propoxy)phenyl]acetate (400 mg, yield 68%) as

a colorless oil.

¹H-NMR (CDCl₃)δ: 1.23 (3H, t, J=6.8 Hz), 1.35 (6H, d, J=6.8 Hz), 2.12-2.17 (2H, m), 2.67 (2H, q, J=6.8 Hz), 2.74 (2H, t, J=8.4 Hz), 3.00-3.10 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.87⁵ (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.10 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.94-7.97 (1H, m), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

Example 227

A mixture of methyl [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (400 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (370 mg, yield 96%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 155-156°C.

Example 228

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-ethyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (490 mg, yield 83%) was obtained as

a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ : 1.03 (3H, t, J=7.2 Hz), 1.23 (3H, t, J=7.6 Hz), 1.73-1.80 (2H, m), 2.11-2.17 (2H, m), 2.64-2.73 (6H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.96 (1H, dd, J=8.8, 2.0 Hz), 8.02 (1H, d, J=8.8 Hz), 8.34 (1H, s), 8.61 (1H, m).

Example 229

A mixture of methyl [3-ethyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (490 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (450 mg, yield 96%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 146-147°C

Example 230

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (570 mg), methyl (3-cyano-2-hydroxyphenyl)acetate (360 mg), tributylphosphine (790 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (980 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-

yl)propoxy)phenyl]acetate (680 mg, yield 75%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 1.35 (6H, d, J=7.2 Hz), 2.14-2.21 (2H, m),
⁵ 2.72-2.76 (2H, m), 3.03-3.09 (1H, m), 3.69 (2H, s), 3.69 (3H, s), 4.32 (2H, t, J=6.0 Hz), 7.13 (1H, t, J=7.6 Hz), 7.48 (1H, dd, J=7.6, 1.6 Hz), 7.54 (1H, dd, J=7.6, 1.6 Hz), 7.95 (1H, dd, J=8.4, 2.8 Hz), 8.04 (1H, d, J=8.4 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

¹⁰ Example 231

A mixture of methyl [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (650 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 95%). The crystals were recrystallized from hexane-ethyl acetate.

²⁰ melting point: 144-145°C

²⁵ Example 232

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (320 mg), methyl (3-cyano-2-hydroxyphenyl)acetate (200 mg), tributylphosphine (440 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-cyano-2-(3-{3-propyl-1-

[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl]propoxyphenyl]acetate (360 mg, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

⁵ ¹H-NMR (CDCl₃)δ: 1.03 (3H, t, J=7.6 Hz), 1.72-1.80 (2H, m), 2.12-2.19 (2H, m), 2.65 (2H, t, J=8.0 Hz), 2.72 (2H, t, J=8.4 Hz), 3.69 (2H, s), 3.70 (3H, s), 4.31 (2H, t, J=6.0 Hz), 7.13 (1H, t, J=8.0 Hz), 7.48 (1H, dd, J=8.0, 1.6 Hz), 7.53 (1H, dd, J=8.0, 1.6 Hz), 7.96 (1H, dd, J=8.4, 2.0 Hz), 8.02 (1H, d, J=8.4 Hz), 8.34 (1H, s), 8.61-8.62 (1H, m).

Example 233

A mixture of methyl [3-cyano-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (330 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-cyano-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (270 mg, yield 86%). The crystals were recrystallized from hexane-ethyl acetate.

²⁵ melting point: 146-147°C

Example 234

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (570 mg), methyl (3-bromo-2-hydroxyphenyl)acetate (460 mg), tributylphosphine (790 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (980 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel

column chromatography, and methyl [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (750 mg, yield 76%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃)δ: 1.35 (6H, d, J=6.8 Hz), 2.14-2.21 (2H, m), 2.76 (2H, t, J=8.4 Hz), 2.60-3.10 (1H, m), 3.69 (3H, s), 3.71 (2H, s), 4.04 (2H, t, J=6.4 Hz), 6.97 (1H, t, J=8.0 Hz), 7.22 (1H, dd, J=8.0, 1.6 Hz), 7.48 (1H, dd, J=8.0, 1.6 Hz), 7.95 (1H, dd, J=8.8, 2.0 Hz), 8.04 (1H, d, J=8.8 Hz), 8.34 (1H, s), 8.60-8.61 (1H, m).

Example 235

A mixture of methyl [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (700 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (610 mg, yield 89%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 146-147°C

Example 236

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (430 mg), methyl (3-bromo-2-hydroxyphenyl)acetate (340 mg), tributylphosphine (590 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was

concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-bromo-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (570 mg, yield 78%) was obtained as
5 a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃)δ: 1.03 (3H, t, J=7.6 Hz), 1.72-1.80 (2H, m),
2.12-2.20 (2H, m), 2.66 (2H, t, J=8.0 Hz), 2.73 (2H, t, J=8.4 Hz),
3.69 (3H, s), 3.70 (2H, s), 4.03 (2H, t, J=6.4 Hz), 6.97
10 (1H, t, J=7.6 Hz), 7.22 (1H, dd, J=7.6, 1.6 Hz), 7.48 (1H, dd,
J=7.6, 1.6 Hz), 7.96 (1H, dd, J=8.8, 2.0 Hz), 8.02 (1H, d,
J=8.8 Hz), 8.34 (1H, s), 8.61-8.62 (1H, m).

Example 237

A mixture of methyl [3-bromo-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (500 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted
15 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-bromo-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-
20 yl}propoxy)phenyl]acetic acid (380 mg, yield 78%). The crystals were recrystallized from hexane-ethyl acetate.
melting point: 145-146°C

Example 238

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (430 mg), methyl (3-chloro-2-hydroxyphenyl)acetate (280 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution
35 was concentrated and isopropyl ether was added. The insoluble

material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (590 mg, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃)δ: 1.35 (6H, d, J=6.8 Hz), 2.11-2.30 (2H, m), 2.74 (2H, t, J=8.0 Hz), 3.04-3.10 (1H, m), 3.69 (3H, s), 3.70 (2H, s), 4.06 (2H, t, J=6.4 Hz), 7.02 (1H, t, J=8.0 Hz), 7.17 (1H, dd, J=8.0, 1.6 Hz), 7.31 (1H, dd, J=8.0, 1.6 Hz), 7.95 (1H, dd, J=8.8, 2.0 Hz), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

Example 239

A mixture of methyl [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (510 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (400 mg, yield 81%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 141-142°C

Example 240

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (460 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (270 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The

reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-ethyl-2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (510 mg, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ : 0.89 (6H, t, J=7.2 Hz), 1.24 (3H, t, J=7.6 Hz), 1.60-1.88 (4H, m), 2.09-2.16 (2H, m), 2.50-2.72 (5H, m), 3.69 (2H, s), 3.69 (3H, s), 3.87 (2H, t, J=6.0 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.95 (1H, dd, J=8.8, 2.4 Hz), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.61 (1H, m).

15 Example 241

A mixture of methyl [3-ethyl-2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (480 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature 4 hours and 1N hydrochloric acid (7 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (350 mg, yield 75%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 130-131°C

30 Example 242

To a mixture of 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (70 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (50 mg), tributylphosphine (110 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (140 mg) at room temperature and the

mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetate (80 mg, yield 69%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹⁰ ¹H-NMR (CDCl₃)δ: 1.24 (3H, t, J=7.6 Hz), 1.34 (6H, d, J=6.8 Hz), 2.05-2.20 (2H, m), 2.56-2.80 (4H, m), 3.04-3.10 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.05-7.16 (2H, m), 7.71 (1H, dd, J=8.8,2.8 Hz), 7.90 (1H, dd, J=8.8,0.8 Hz), 8.24 (1H, s), 8.29 (1H, m).

¹⁵ **Example 243**

A mixture of methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetate (80 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetic acid (50 mg, yield 62%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 142-143°C.

Example 244

³⁰ To a mixture of 3-(3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)-1-propanol (300 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (190 mg), tributylphosphine (410 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (520 mg) at room temperature and the mixture was stirred overnight at 65°C. The

reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (250 mg, yield 53%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl_3) δ : 1.24 (3H, t, $J=7.6$ Hz), 1.35 (6H, d, $J=6.8$ Hz), 2.10-2.19 (2H, m), 2.65-2.72 (2H, m), 2.77 (2H, q, $J=7.6$ Hz), 3.05-3.11 (1H, m), 3.68 (2H, s), 3.69 (3H, s), 3.89 (2H, t, $J=6.0$ Hz), 7.05 (1H, t, $J=7.6$ Hz), 7.11 (1H, dd, $J=7.6, 1.6$ Hz), 7.15 (1H, dd, $J=7.6, 1.6$ Hz), 7.84 (1H, d, $J=9.2$ Hz), 8.30 (1H, d, $J=9.2$ Hz), 8.55 (1H, s).

¹⁵ **Example 245**

A mixture of methyl [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (220 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (7 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (140 mg, yield 67%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 126-127°C.

³⁰ **Example 246**

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (150 mg), tributylphosphine (330 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (410 mg) at room temperature and the

mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (210 mg, yield 54%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

10 ¹H-NMR (CDCl_3) δ : 1.24 (3H, t, $J=7.6$ Hz), 1.34 (6H, d, $J=7.2$ Hz), 2.05-2.17 (2H, m), 2.64-2.74 (4H, m), 3.02-3.09 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, $J=6.4$ Hz), 7.04 (1H, t, $J=7.6$ Hz), 7.10 (1H, dd, $J=7.6, 1.6$ Hz), 7.15 (1H, dd, $J=7.6, 1.6$ Hz), 7.84-7.85 (2H, m), 8.24 (1H, s), 8.38-8.39 (1H, m).

15

Example 247

A mixture of methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (190 mg), 1N aqueous sodium hydroxide solution (2 ml), ²⁰ tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (140 mg, yield 76%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 152°C.

25

Example 248

To a mixture of 3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (140 mg), tributylphosphine (310 mg) and tetrahydrofuran (20 ml) was ³⁵ added 1,1'-azodicarbonyldipiperidine (390 mg) at room

temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [2-(3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)-3-ethylphenyl]acetate (180 mg, yield 48%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

10 ¹H-NMR (CDCl₃)δ: 1.24 (3H, t, J=7.6 Hz), 1.37 (6H, d, J=7.2 Hz), 2.02-2.18 (2H, m), 2.64-2.77 (4H, m), 3.06-3.12 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.88 (2H, t, J=6.4 Hz), 7.05 (1H, t, J=7.6 Hz), 7.10-7.12 (1H, m), 7.15 (1H, dd, J=7.6, 2.0 Hz), 8.08 (2H, m), 8.62 (1H, m).

15 **Example 249**

A mixture of methyl [2-(3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)-3-ethylphenyl]acetate (160 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)-3-ethylphenyl]acetic acid (90 mg, yield 58%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 93-95°C.

30 **Example 250**

To a mixture of 3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (160 mg), tributylphosphine (340 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (430 mg) at room temperature and the

mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (260 mg, yield 67%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹⁰ ¹H-NMR (CDCl₃)δ: 1.23 (3H, t, J=7.6 Hz), 1.36 (6H, d, J=6.8 Hz), 2.10-2.16 (2H, m), 2.67 (2H, q, J=7.6 Hz), 2.74 (2H, t, J=8.4 Hz), 3.06-3.13 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.87 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6,1.6 Hz), 7.15 (1H, dd, J=7.6,1.6 Hz), 7.87 (1H, d, J=2.4 Hz), 7.89 (1H, s), 8.35-8.36 (1H, m).

Example 251

A mixture of methyl (2-{3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (230 mg), 1N aqueous sodium hydroxide solution (3 ml), ²⁰ tetrahydrofuran (3 ml) and methanol (3 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The ²⁵ obtained colorless crystals were collected by filtration to give (2-{3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (180 mg, yield 81%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 93-95°C.

³⁰ **Example 252**

To a mixture of 3-[1-(5-chloro-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (530 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (340 mg), tributylphosphine (740 mg) and tetrahydrofuran (30 ml) was added 1,1'-³⁵ azodicarbonyldipiperidine (920 mg) at room temperature and the

mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetate (440 mg, yield 53%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹⁰ ¹H-NMR (CDCl_3) δ : 0.88 (6H, t, $J=7.6$ Hz), 1.23 (3H, t, $J=7.6$ Hz), 1.70-1.79 (4H, m), 2.10-2.13 (2H, m), 2.55-2.71 (5H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, $J=6.4$ Hz), 7.04 (1H, t, $J=7.6$ Hz), 7.12 (1H, dd, $J=7.6, 2.0$ Hz), 7.15 (1H, dd, $J=7.6, 2.0$ Hz), 7.70 (1H, dd, $J=8.8, 2.4$ Hz), 7.89 (1H, dd, $J=8.8, 0.4$ Hz), 8.24 (1H, s), 8.29-8.30 (1H, m).

Example 253

A mixture of methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetate (440 mg), 1N aqueous sodium hydroxide solution (3 ml), ²⁰ tetrahydrofuran (3 ml) and methanol (3 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The ²⁵ obtained colorless crystals were collected by filtration to give (2-(3-[1-(5-chloro-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetic acid (300 mg, yield 70%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 114-115°C

Example 254

To a solution of 4-propyl-3-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazole (400 mg) in N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 46 mg) at 0°C and the mixture was ³⁵ stirred at room temperature for 15 minutes. Bromomethyl

acetate (0.10 ml) was added at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and white crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained crystal, 1N aqueous sodium hydroxide solution (1.5 ml),
5 tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The
10 obtained colorless crystals were collected by filtration to give [4-propyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-1-yl]acetic acid (310 mg, yield 69%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.
15
20 **Example 255**

To a solution of 3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-4-propyl-1H-pyrazole (400 mg) in N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 46 mg) at 0°C and the mixture was stirred at room
25 temperature for 15 minutes. Bromomethyl acetate (0.10 ml) was added at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried
30 (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and white crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained crystal, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and
35 methanol (4 ml) was stirred at room temperature 5 hours. 1N

Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-propyl-1H-pyrazol-1-yl]acetic acid (330 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

10 Example 256

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (370 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (240 mg, yield 35%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 164-165°C.

Example 257

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (370 mg),

tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (270 mg, yield 40%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 89-90°C.

Example 258

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (230 mg), ethyl (2-fluoro-3-hydroxyphenyl)acetate (140 mg), tributylphosphine (280 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (350 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were

collected by filtration to give [2-fluoro-3-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (220 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane.
5 melting point: 109-110°C.

Example 259

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine
10 (640 mg) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
15 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2.5 ml) was added, and the mixture was
20 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
25 yl)propoxy)phenyl]acetic acid (590 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane.
melting point: 122-123°C.

Example 260

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (620 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (420 mg), tributylphosphine
30 (800 mg) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (1.00 g) at room temperature and the mixture was stirred overnight. The reaction solution was
35 concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethoxy-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (880 mg, yield 90%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 133-134°C.

15 Example 261

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (300 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (300 mg, yield 46%). The crystals were recrystallized from ethyl acetate-

hexane. melting point: 190-191°C.

Example 262

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(1-
5 cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (340 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was
added 1,1'-azodicarbonyldipiperidine (650 mg) at room
temperature and the mixture was stirred overnight. The
reaction solution was concentrated. The residue was subjected
10 to silica gel column chromatography, and a colorless oil was
obtained from a fraction eluted with ethyl acetate-hexane
(1:4, volume ratio). A mixture of the obtained oily substance,
1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran
(4 ml) and methanol (4 ml) was stirred at room temperature for
15 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture
was extracted with ethyl acetate. The ethyl acetate layer was
washed with saturated aqueous sodium chloride solution, dried
(MgSO₄) and concentrated. The obtained colorless crystals were
collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-
20 isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-
yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (230 mg, yield
34%). The crystals were recrystallized from ethyl acetate-
hexane. melting point: 166-167°C.

Example 263

25 To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (350 mg), ethyl 3-[3-
hydroxy-1-isopropyl-1H-pyrazol-5-yl]propanoate (250 mg), tributylphosphine (440 mg) and tetrahydrofuran (50 ml) was
added 1,1'-azodicarbonyldipiperidine (560 mg) at room
30 temperature and the mixture was stirred overnight. The
reaction solution was concentrated. The residue was subjected
to silica gel column chromatography, and a colorless oil was
obtained from a fraction eluted with ethyl acetate-hexane
(1:4, volume ratio). A mixture of the obtained oily substance,
35 1N aqueous sodium hydroxide solution (1 ml), tetrahydrofuran

(4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
5 solution, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-isopropyl-3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-5-yl]propanoic acid (200 mg, yield 36%). The crystals were recrystallized from ethyl
10 acetate-hexane. melting point: 130-131°C.

Example 264

A mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (390 mg), 1N aqueous sodium hydroxide solution (1.5 ml),
15 tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours, and concentrated. To a mixture of the obtained residue and water (10 ml) was added a solution of calcium chloride (0.20 g) in water (1 ml) at room temperature and the mixture was stirred overnight. The resulting white
20 precipitates were collected by filtration to give calcium (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (300 mg, yield 81%) as amorphous.

¹H-NMR (DMSO-d₆) δ : 1.23 (6H, d, J=6.6 Hz), 1.85-1.98 (2H, m),
25 2.60 (2H, t, J=7.4 Hz), 2.96 (1H, septet, J=6.9 Hz), 3.37 (2H, s), 3.73 (3H, s), 3.91 (2H, t, J=6.2 Hz), 5.29 (2H, br s), 6.75-6.90 (3H, m), 7.08 (1H, dd, J=8.6, 2.9 Hz), 7.51 (1H, d, J=8.4 Hz), 7.72 (1H, d, J=2.4 Hz), 8.10 (1H, s).

Example 265

30 To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (390 mg) and N,N-dimethylformamide (6 ml) was added acetic anhydride (0.10 ml) at room temperature and the mixture was stirred overnight. Water (20 ml) was added to the reaction
35 mixture and the mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated. A mixture of the obtained residue, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-acetylamino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (320 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 158-159°C.

Example 266

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (400 mg) and N,N-dimethylformamide (6 ml) was added propionyl chloride (0.12 ml) at 0°C and the mixture was stirred at room temperature overnight. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-1-(5-propanoylamino-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (340 mg, yield 78%). The crystals were recrystallized from ethyl

acetate-hexane. melting point: 147-148°C.

Example 267

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl) acetate (400 mg) and N,N-dimethylformamide (6 ml) was added butyryl chloride (0.14 ml) at 0°C and the mixture was stirred at room temperature overnight. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-butyrylamino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl) acetic acid (350 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 119-120°C.

Example 268

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl) acetate (400 mg) and N,N-dimethylformamide (6 ml) was added isobutyryl chloride (0.15 ml) at 0°C and the mixture was stirred at room temperature overnight. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-

hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added
5 and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-[3-isopropyl-1-[5-(2-
10 methylpropanoylamino)-2-pyridyl]-1H-pyrazol-4-yl]propoxy)phenyl]acetic acid (370 mg, yield 82%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.

Example 269

15 To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (400 mg), pyridine (0.10 ml) and acetonitrile (6 ml) was added methanesulfonyl chloride (0.10 ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. Water (15 ml) was
20 added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
25 fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was
30 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-1-(5-methylsulfonylamino-2-pyridyl)-1H-pyrazol-4-
35 yl]propoxy)phenyl]acetic acid (270 mg, yield 58%). The

crystals were recrystallized from ethanol. melting point: 176-177°C.

Example 270

A mixture of methyl (3-methoxy-2-{3-[3-isopropyl-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate (400 mg), 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (240 mg, yield 62%).
The crystals were recrystallized from ethanol. melting point: 161-162°C.

Example 271

To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridine-3-carbonitrile (520 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (380 mg), tributylphosphine (780 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (970 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(5-cyano-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid

(460 mg, yield 67%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145°C.

⁵ Example 272

To a mixture of 3-[3-isopropyl-1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (300 mg), tributylphosphine (620 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (780 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).
¹⁰ A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
¹⁵ washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-(3-[3-isopropyl-1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]propoxy)phenyl)acetic acid (470 mg, yield 72%). The crystals were recrystallized
²⁰ from ethyl acetate-hexane. melting point: 132-133°C.
²⁵

Example 273

To a mixture of 3-[1-(5-fluoro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (410 mg), tributylphosphine (770 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (960 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a
³⁰ fraction eluted with ethyl acetate-hexane (1:4, volume ratio).
³⁵

A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-fluoro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (180 mg, yield 22%). The crystals were recrystallized from ethanol-hexane. melting point: 125-126°C.

Example 274

To a mixture of 3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (490 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 92-93°C.

Example 275

To a mixture of 3-{3-isopropyl-1-[5-

(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), benzyl (2-hydroxy-3-methoxyphenyl)acetate (450 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (0.1 g) and tetrahydrofuran (8 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [3-methoxy-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (390 mg, yield 65%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

Example 276

To a mixture of 3-[1-(5-ethylpyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine (590 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (740 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-[3-[1-(5-ethylpyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy]-3-methoxyphenyl)acetic acid (430 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 103-104°C.

Example 277

To a mixture of 3-[1-(6-methoxypyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine (440 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-[3-[1-(6-methoxypyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy]phenyl)acetic acid (400 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 124-125°C.

Example 278

To a mixture of 3-[1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (400 mg), ethyl (4-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine (520 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

10 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-4-(3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (250 mg, yield 41%). The

15 crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

Example 279

To a mixture of 3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (300 mg), tributylphosphine (520 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours.

20 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-4-(3-{1-[5-

25 (trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-

30

35

yl)propoxy)phenyl]propanoic acid (220 mg, yield 35%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 118-119°C.

Example 280

5 To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (320 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (740 mg) at room temperature and the
10 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium
15 hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried
20 ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and 6-(4-{3-[2-methoxy-6-(methoxycarbonylmethyl)phenoxy]propyl}-3-isopropyl-1H-pyrazol-1-yl)pyridazine-3-carboxylic acid (220 mg, yield 32%) was obtained as colorless crystals from a fraction eluted with
25 ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 146-147°C.

Example 281

To a mixture of 3-[3-isopropyl-1-(5-chloro-2-pyridinyl)-
30 1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (261 mg), tributylphosphine (713 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (722 mg) at room temperature and the mixture was stirred for 2.5 days. The reaction solution was
35 concentrated. The residue was subjected to silica gel column

chromatography, and methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)phenyl)acetate (470 mg, yield 77%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio).

¹H-NMR (CDCl₃) δ: 1.32 (6H, d, J = 6.9 Hz), 2.02 – 2.18 (2H, m), 2.62 – 2.71 (2H, m), 2.95 – 3.10 (1H, m), 3.65 (2H, s), 3.67 (3H, s), 4.00 – 4.06 (2H, m), 6.80 – 6.94 (2H, m), 7.15 – 7.27 (2H, m), 7.69 (1H, dd, J = 2.7, 9.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.19 (1H, s), 8.27 (1H, d, J = 2.7 Hz).

Example 282

To a mixture of 3-[3-isopropyl-1-(5-chloro-2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (308 mg), tributylphosphine (713 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (722 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetate (550 mg, yield 84%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio).

¹H-NMR (CDCl₃) δ: 1.33 (6H, d, J = 6.9 Hz), 2.01 – 2.12 (2H, m), 2.64 – 2.72 (2H, m), 2.97 – 3.12 (1H, m), 3.66 (3H, s), 3.68 (2H, s), 3.83 (3H, s), 4.02 – 4.09 (2H, m), 6.78 – 6.86 (2H, m), 6.96 – 7.03 (1H, m), 7.68 (1H, dd, J = 2.7, 9.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.23 (1H, s), 8.27 (1H, d, J = 2.7 Hz).

Example 283

To a mixture of 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (367 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (200 mg), tributylphosphine (588 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (596 mg) at room

temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained pale-red solid was recrystallized from ethyl acetate to give [1-methyl-3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]acetic acid (222 mg, yield 44%) as colorless crystals. melting point: 143-144°C.

Example 284

To a mixture of 2-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-ethanol (356 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (200 mg), tributylphosphine (588 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (596 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl

acetate-hexane (7:3, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-1-methyl-1H-pyrazol-5-yl]acetic acid (104 mg, yield 5 20%) as colorless crystals. melting point: 156-158°C.

Example 285

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (392 mg), tributylphosphine 10 (792 µL) and tetrahydrofuran (32 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction 15 eluted with ethyl acetate-hexane (1:5, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give methyl 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (174 mg, yield 34%) as colorless crystals. melting point: 79-81°C.

20 **Example 286**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (3-hydroxyphenyl)acetate (529 mg), tributylphosphine (792 µL) and tetrahydrofuran (32 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A 25 mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 30 saturated aqueous sodium chloride solution, dried ($MgSO_4$) and 35

concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (524 mg, yield 73%) as colorless
5 crystals. melting point: 128-130°C.

Example 287

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 3-(3-ethoxy-4-hydroxyphenyl)propanoate (393 mg), tributylphosphine (792 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-
25 methoxyphenyl]propanoic acid (403 mg, yield 51%) as colorless crystals. melting point: 111-112°C.

Example 288

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (2-hydroxyphenyl)acetate (291 mg), tributylphosphine (792 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction

eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (479 mg, yield 67%) as colorless crystals. melting point: 121-122°C.

Example 289

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropaneacetate (393 mg), tributylphosphine (792 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained oily substance was recrystallized from ethyl acetate-hexane to give 2-[3-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropanoic acid (140 mg, yield 18%)

as colorless crystals. melting point: 98–99°C.

Example 290

To a mixture of ethyl 2-(3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy)-2-methylpropanoate (400 mg), 2-chloro-3-⁵ (trifluoromethyl)pyridine (240 mg) and N,N-dimethylformamide (20 ml) was added sodium hydride (60%, in oil, 52.8 mg) at 0°C and the mixture was stirred at room temperature for 3 hours. Thereafter, to the reaction solution was added ethyl iodide (106 µL), and the mixture was stirred for 2.5 hours. To the ¹⁰ reaction solution was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column ¹⁵ chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N ²⁰ Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. A mixture of the obtained colorless oil, 1N aqueous sodium hydroxide solution (325 µL), ²⁵ tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (36.0 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The ³⁰ resulting white precipitates were collected by filtration to give calcium 2-[3-(3-(3-ethoxy-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (166 mg, yield 31%) as amorphous.

³⁵ 1H -NMR (DMSO-d₆) δ: 1.33 (3H, t, J = 7.2 Hz), 1.41 (6H, s), 1.92 – 2.04 (2H, m), 2.45 – 2.55 (2H, m), 3.88 – 3.96 (2H, m),

4.24 (2H, q, $J = 7.2$ Hz), 6.36 – 6.45 (3H, m), 6.96 – 7.04 (1H, m), 7.44 – 7.51 (1H, m), 8.19 (1H, s), 8.29 – 8.35 (1H, m), 8.63 – 8.68 (1H, m).

Example 291

5 A mixture of ethyl 2-[3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (400 mg), 3-(trifluoromethyl)phenylboric acid (418 mg), copper(II) acetate (300 mg), pyridine (160 μ L) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction
10 solution was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and
15 a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml)
20 was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl
25 acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (610 μ L), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium
30 chloride (67.6 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-[3-(3-(3-ethoxy-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (343 mg,
35 yield 63%) as amorphous.

¹H-NMR (DMSO-d₆) δ: 1.34 (3H, t, J = 7.0 Hz), 1.41 (6H, s), 1.90 – 2.07 (2H, m), 2.42 – 2.54 (2H, m), 3.88 – 4.00 (2H, m), 4.29 (2H, q, J = 7.0 Hz), 6.36 – 6.46 (3H, m), 6.96 – 7.07 (1H, m), 7.45 – 7.53 (1H, m), 7.59 – 7.70 (1H, m), 7.95 – 8.04 (2H, m), 8.41 (1H, s).

Example 292

A mixture of ethyl 2-[3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (400 mg), 2-(trifluoromethyl)phenylboric acid (418 mg), copper(II) acetate (10 mg), pyridine (160 μL) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction solution was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (265 μL), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (29.3 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-[3-(3-(3-ethoxy-1-[2-(trifluoromethyl)phenyl]-

1H-pyrazol-4-yl)propoxy)phenoxy]-2-methylpropanoate (109 mg, yield 20%) as amorphous.

¹H-NMR (DMSO-d₆) δ: 1.30 (3H, t, J = 7.0 Hz), 1.41 (6H, s), 1.86 – 2.04 (2H, m), 2.42 – 2.54 (2H, m), 3.86 – 3.98 (2H, m),
⁵ 4.19 (2H, q, J = 7.0 Hz), 6.35 – 6.47 (3H, m), 6.96 – 7.06 (1H, m), 7.53 – 7.65 (2H, m), 7.68 – 7.90 (3H, m).

Example 293

A mixture of ethyl 2-[3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (400 mg), 4-
¹⁰ ethylphenylboric acid (318 mg), copper(II) acetate (289 mg), pyridine (154 μL) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction solution was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The ethyl acetate
¹⁵ layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily
²⁰ substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous
²⁵ sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (600 μL),
³⁰ tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (66.2 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The
³⁵ resulting white precipitates were collected by filtration to

give calcium 2-(3-[3-[3-ethoxy-1-(4-ethylphenyl)-1H-pyrazol-4-yl]propoxy]phenoxy)-2-methylpropanoate (274 mg, yield 55%) as amorphous.

¹H-NMR (DMSO-d₆) δ: 1.18 (3H, t, J = 7.8 Hz), 1.33 (3H, t, J = 7.0 Hz), 1.41 (6H, s), 1.88 – 2.06 (2H, m), 2.40 – 2.55 (2H, m), 2.59 (2H, q, J = 7.8 Hz), 3.86 – 3.98 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 6.35 – 6.46 (3H, m), 6.95 – 7.07 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 8.13 (1H, s).

Example 294

A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (400 mg), 4-methylphenylboric acid (288 mg), copper(II) acetate (289 mg), pyridine (154 μL) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction solution was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:8, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (775 μL), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (86.0 mg) dissolved in a small amount of water and

the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-(3-{3-[3-ethoxy-1-(4-methylphenyl)-1H-pyrazol-4-yl]propoxy}phenoxy)-2-methylpropanoate (353 mg, yield 73%)
as amorphous.

¹H-NMR (DMSO-d₆) δ: 1.32 (3H, t, J = 7.0 Hz), 1.41 (6H, s),
1.88 – 2.04 (2H, m), 2.29 (3H, s), 2.40 – 2.53 (2H, m), 3.86 –
3.98 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 6.35 – 6.47 (3H, m),
6.95 – 7.08 (1H, m), 7.21 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J
= 8.4 Hz), 8.13 (1H, s).

Example 295

To a mixture of 4-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-butanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (330 mg), tributylphosphine (762 μL) and tetrahydrofuran (120 ml) was added 1,1'-azodicarbonyldipiperidine (772 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-methoxy-2-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (451 mg, yield 60%) as colorless crystals. melting point: 111–112°C.

Example 296

To a mixture of 3-(3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (234 mg), tributylphosphine

(638 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred for 2 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 2.5 days.

10 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-{3-propyl-1-[4-

15 (trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (340 mg, yield 59%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

1H-NMR ($CDCl_3$) δ : 0.99 (3H, t, J = 7.4 Hz), 1.60 – 1.82 (2H, m), 1.91 – 2.08 (2H, m), 2.54 – 2.68 (4H, m), 3.65 (2H, s), 3.90 – 4.00 (2H, m), 6.74 – 6.92 (2H, m), 7.08 – 7.26 (2H, m), 7.54 – 7.73 (5H, m).

Example 297

To a mixture of 3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (290 mg), tributylphosphine (668 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (676 mg) at room temperature and the mixture was stirred overnight for 2.5 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred

overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The obtained solid was recrystallized from diisopropyl ether-hexane to give [3-methoxy-2-(3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (472 mg, yield 74%) as colorless crystals. melting point: 95-96°C.

Example 298

A mixture of methyl 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (86.3 mg), 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 8 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (67.3 mg, yield 80%) as colorless crystals. melting point: 119-120°C.

Example 299

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (240 mg), tributylphosphine (638 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane

(1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the 5 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H- 10 pyrazol-4-yl)propoxy]-1-methyl-1H-pyrazol-4-yl]acetic acid (441 mg, yield 76%) as colorless crystals. melting point: 122-123°C.

Example 300

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (424 mg), tributylphosphine (638 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The reaction solution was 20 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and 25 ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was 30 recrystallized from ethyl acetate-hexane to give [3-ethoxy-2-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (455 mg, yield 72%) as colorless crystals. melting point: 141-142°C.

Example 301

35 To a mixture of 3-(3-ethoxy-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (420 mg), tributylphosphine (633 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-ethoxy-2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (415 mg, yield 66%) as colorless crystals. melting point: 114-115°C.

20 Example 302

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (206 mg), tributylphosphine (563 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and

concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (345 mg, yield 63%) as colorless
5 crystals. melting point: 127-128°C.

Example 303

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (211 mg),
10 tributylphosphine (563 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was
15 obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture
20 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-
25 yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (457 mg, yield 82%) as colorless crystals. melting point: 157-158°C.

Example 304

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (3-hydroxy-4-methoxyphenyl)acetate (261 mg), tributylphosphine (563 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction
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eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (268 mg, yield 46%) as colorless crystals. melting point: 117-118°C.

Example 305

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (170 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (100 mg), tributylphosphine (272 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (275 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (15 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (15 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [1-ethyl-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-4-yl]acetic acid (117 mg, yield 46%) as colorless crystals. melting point: 105-106°C.

Example 306

To a mixture of 3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (466 mg), tributylphosphine (703 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-ethoxyphenyl]acetic acid (537 mg, yield 72%) as colorless crystals. melting point: 156-157°C.

20 Example 307

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (243 mg), tributylphosphine (563 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and

concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-3-methoxyphenyl]acetic acid (427 mg, yield 73%) as colorless
5 crystals. melting point: 140-141°C.

Example 308

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetate (230 mg), 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20
10 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white
15 solid was recrystallized from ethyl acetate-hexane to give (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (182 mg, yield 82%) as colorless crystals. melting point: 141-142°C.

Example 309

20 A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetate (240 mg), 5% palladium-carbon (100 mg) and ethanol (50 ml) was stirred at room temperature for 2 days under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate
25 was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and
30 ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was
35 recrystallized from ethyl acetate-hexane to give (2-{3-[3-

isopropyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxyphenyl)acetic acid (92.4 mg, yield 43%) as colorless crystals. melting point: 140-142°C.

Example 310

5 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (354 mg), methyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propanoate (246 mg), tributylphosphine (563 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,
15 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride
20 solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1-methyl-1H-pyrazol-4-yl]propanoic acid (307 mg, yield 58%) as colorless crystals. melting point: 124-
25 125°C.

Example 311

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (260 mg), 1N aqueous sodium hydroxide solution (20 ml),
30 tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-

hexane to give (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetic acid (214 mg, yield 85%) as colorless crystals. melting point: 148-149°C.

Example 312

5 A mixture of methyl (2-(3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetate (290 mg), 5% palladium-carbon (300 mg) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the
10 filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran
15 (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained
20 colorless oil was recrystallized from diisopropyl ether-hexane to give (2-(3-[3-isopropyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetic acid (82.0 mg, yield 32%) as colorless crystals. melting point: 102-104°C.

Example 313

25 To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (170 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (100 mg), tributylphosphine (272 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (275 mg) at room
30 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained
35 oily substance, 1N aqueous sodium hydroxide solution (20 ml),

tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (3:2, volume ratio). The obtained solid was recrystallized from diisopropyl ether-hexane to give [1-ethyl-⁵ 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-4-yl]acetic acid (105 mg, yield 42%) as colorless crystals. melting point: 99-100°C.

Example 314

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propanoate (278 mg), tributylphosphine (638 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[1-methyl-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-4-yl]propanoic acid (436 mg, yield 73%) as colorless crystals. melting point: 103-104°C.

Example 315

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (313 mg), methyl (2-hydroxy-3-methylphenyl)acetate (541 mg), tributylphosphine (748 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (757 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred at said temperature for 1 hour. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (7:13, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [2-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-3-methylphenyl]acetic acid (135 mg, yield 29%) as colorless crystals. melting point: 159-160°C.

Example 316

To a mixture of 3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (305 mg), tributylphosphine (703 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium

hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (193 mg, yield 27%) as colorless crystals. melting point: 184-185°C.

Example 317

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (329 mg), ethyl (1-cyclohexyl-3-hydroxy-1H-pyrazol-4-yl)acetate (250 mg), tributylphosphine (523 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (530 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained oily substance was recrystallized from ethyl acetate-hexane to give

[1-cyclohexyl-3-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-4-yl]acetic acid (145 mg, yield 27%) as colorless crystals. melting point: 116-117°C.

5 Example 318

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (450 mg), ethyl (5-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (292 mg), tributylphosphine (716 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [5-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (246 mg, yield 38%) as colorless crystals. melting point: 146-148°C.

Example 319

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (344 mg), tributylphosphine (792 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography,

and a pale yellow solid was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred 5 overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-
10 hexane to give [3-methyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (268 mg, yield 37%) as colorless crystals. melting point: 134-135°C.

Example 320

15 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (1-cyclohexyl-3-hydroxy-1H-pyrazol-4-yl)acetate (336 mg), tributylphosphine (638 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room
20 temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume
25 ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was
30 washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow solid was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained solid was recrystallized
35 from ethyl acetate-hexane to give [1-cyclohexyl-3-(3-

propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-4-yl]acetic acid (453 mg, yield 68%) as colorless crystals. melting point: 127-128°C.

Example 321

5 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (450 mg), ethyl (5-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (291 mg), tributylphosphine (718 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room
10 temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane
15 (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate
20 layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [1-methyl-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (274 mg,
25 yield 42%) as colorless crystals. melting point: 136-138°C.

Example 322

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl (1-ethyl-5-hydroxy-1H-pyrazol-4-yl)acetate (381 mg),
30 tributylphosphine (797 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica
35 gel column chromatography, and a pale-yellow oily substance

was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [1-ethyl-5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (187 mg, yield 25%) as colorless crystals. melting point: 120-121°C.

Example 323

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(2-hydroxy-3-methoxyphenyl)propanoate (395 mg), tributylphosphine (797 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-

methoxyphenyl]propanoic acid (429 mg, yield 55%) as colorless crystals. melting point: 112–113°C.

Example 324

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-4-methoxyphenyl)propanoate (395 mg), tributylphosphine (797 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate–hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The obtained white solid was recrystallized from ethyl acetate–hexane to give 3-[3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-4-methoxyphenyl]propanoic acid (447 mg, yield 57%) as colorless crystals. melting point: 93–94°C.

Example 325

To a mixture of 3-(3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl (5-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (286 mg), tributylphosphine (703 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate–hexane (3:7, volume

ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was
5 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [5-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-
10 4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (538 mg, yield 78%) as colorless crystals. melting point: 137-138°C.

Example 326

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl (1-
15 ethyl-5-hydroxy-1H-pyrazol-4-yl)acetate (349 mg), tributylphosphine (797 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction
20 solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran
25 (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [1-ethyl-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (431 mg, yield 58%) as colorless crystals. melting point: 125-126°C.

35 Example 327

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (5-hydroxy-4-methyl-1H-pyrazol-1-yl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a brown solid was obtained from a fraction eluted with methanol-ethyl acetate (1:19, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methyl-1H-pyrazol-1-yl]acetic acid (222 mg, yield 37%) as colorless crystals. melting point: 123-124°C.

Example 328

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (349 mg), tributylphosphine (797 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume

ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 30 minutes. 1N Hydrochloric acid (25 ml) was added, and the 5 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [4-ethyl-5-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-
10 1H-pyrazol-4-yl)propoxy]-1H-pyrazol-1-yl]acetic acid (635 mg, yield 85%) as colorless crystals. melting point: 111-112°C.

Example 329

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl (5-
15 hydroxy-4-methyl-1H-pyrazol-1-yl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction
20 solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and
25 ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was
30 recrystallized from ethyl acetate-hexane to give [4-methyl-5-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy]-1H-pyrazol-1-yl]acetic acid (433 mg, yield 75%) as colorless crystals. melting point: 145-146°C.

Example 330

35 To a mixture of 3-(3-(1-ethylpropyl)-1-[5-

(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (318 mg), tributylphosphine (728 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (737 mg) at room
5 temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane
10 (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 30 minutes. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl
15 acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless oil was recrystallized from ethyl acetate-hexane to give [4-ethyl-5-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-
20 pyrazol-1-yl]acetic acid (389 mg, yield 54%) as colorless crystals. melting point: 124-125°C.

Example 331

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (4-
25 ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (279 mg), tributylphosphine (638 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred at said temperature for 8 hours. The reaction
30 solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and
35 ethanol (25 ml) was stirred at room temperature for 1 hour. 1N

Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [4-ethyl-5-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-1-yl]acetic acid (420 mg, yield 71%) as colorless crystals. melting point: 135-136°C.

Example 332

To a mixture of 1-{6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]-3-pyridinyl}ethanone (320 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (239 mg), tributylphosphine (553 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (560 mg) at room temperature and the mixture was stirred for 3 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give (2-{3-[1-(5-acetyl-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (299 mg, yield 60%) as colorless crystals. melting point: 148-149°C.

Example 333

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (297 mg), tributylphosphine (728 μ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (737 mg) at room

temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and [1-ethyl-3-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (520 mg, yield 72%) was obtained as amorphous from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (6H, t, J = 7.2 Hz), 1.40 (3H, t, J = 7.2 Hz), 1.60 – 1.83 (4H, m), 2.01 – 2.13 (2H, m), 2.52 – 2.67 (3H, m), 3.44 (2H, s), 3.96 (2H, q, J = 7.2 Hz), 4.21 – 4.28 (2H, m), 7.20 (1H, s), 7.90 – 7.96 (1H, m), 8.02 (1H, d, J = 8.4 Hz), 8.31 (1H, s), 8.56 – 8.60 (1H, m).

Example 334

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (310 mg), tributylphosphine (762 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture

was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-
5 butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-
yl}propoxy)-1-ethyl-1H-pyrazol-4-yl]acetic acid (403 mg, yield
55%) as colorless crystals. melting point: 109-110°C.

Example 335

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-
10 pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (1-
ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (322 mg),
tributylphosphine (792 μ L) and tetrahydrofuran (100 ml) was
added 1,1'-azodicarbonyldipiperidine (802 mg) at room
temperature and the mixture was stirred overnight. The
15 reaction solution was concentrated. The residue was subjected
to silica gel column chromatography, and a colorless oil was
obtained from a fraction eluted with ethyl acetate-hexane
(1:3, volume ratio). A mixture of the obtained oily substance,
1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran
20 (25 ml) and ethanol (25 ml) was stirred at room temperature
for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the
mixture was extracted with ethyl acetate. The ethyl acetate
layer was washed with saturated aqueous sodium chloride
solution, dried ($MgSO_4$) and concentrated. The obtained white
25 solid was recrystallized from ethyl acetate-hexane to give [3-{3-
(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-
yl}propoxy)-1-ethyl-1H-pyrazol-4-yl]acetic acid (398 mg, yield
54%) as colorless crystals. melting point: 108-109°C.

Example 336

30 To a mixture of 3-[1-(3,5-dichloro-2-pyridyl)-3-
isopropyl-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-
hydroxy-3-methoxyphenyl)acetate (315 mg), tributylphosphine
(645 mg) and tetrahydrofuran (60 ml) was added 1,1'-
azodicarbonyldipiperidine (805 mg) at room temperature and the
35 mixture was stirred overnight. The reaction solution was

concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at 50°C for 2 hours and poured into water. 2N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(3,5-dichloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (550 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

Example 337

To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (430 mg), tributylphosphine (740 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(6-cyanopyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-

methoxyphenyl)acetic acid (300 mg, yield 37%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

5 Example 338

To a mixture of 2-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyrimidine-5-carbonitrile (330 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).
10 A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(5-cyanopyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (140 mg, yield 28%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 167-168°C.
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Example 339

To a mixture of 3-(3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)-1-propanol (700 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (480 mg), tributylphosphine (820 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
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obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (4 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (760 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 81-82°C.

Example 340

To a mixture of 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (700 mg), methyl (2-hydroxy-3-methylphenyl)acetate (440 mg), tributylphosphine (820 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (4 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (730 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 76-77°C.

Example 341

To a mixture of 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (280 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (180 mg),
5 tributylphosphine (330 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (410 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was
10 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture
15 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-
20 4-yl)propoxy]phenylacetic acid (250 mg, yield 60%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 93-94°C.

Example 342

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propanol (550 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (350 mg), tributylphosphine (710 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred
30 while heating under reflux for 6 hours. Water (20 ml) was
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added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (180 mg, yield 22%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 163-164°C.

Example 343

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propanol (610 mg), methyl (2-hydroxy-3-methylphenyl)acetate (360 mg), tributylphosphine (720 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (900 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (260 mg, yield 30%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 110-111°C.

Example 344

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-

1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (270 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours, and 1N hydrochloric acid (2 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (131 mg, yield 22%) as colorless crystals. The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

Example 345

To a mixture of 3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (330 mg), tributylphosphine (762 μl) and tetrahydrofuran (75 ml) was added 1,1'-azodicarbonyldipiperidine (772 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and 1N hydrochloric acid (25 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless oil was crystallized from hexane to give [2-(3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (511 mg, 5 yield 68%) as colorless crystals. melting point: 94-95°C.

Example 346

To a mixture of 3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (2-hydroxy-3-methylphenyl)acetate (230 mg), tributylphosphine (10 578 μl) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (585 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from (15 a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and 1N hydrochloric acid (25 ml) was added. The mixture was (20 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained pale-yellow oily substance was crystallized from hexane to give [2-(3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (25 236 mg, yield 43%) as colorless crystals. melting point: 86-87°C.

Example 347

To a mixture of 3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (3-30 ethyl-2-hydroxyphenyl)acetate (326 mg), tributylphosphine (762 μl) and tetrahydrofuran (75 ml) was added 1,1'-azodicarbonyldipiperidine (772 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column (35 chromatography, and a yellow oily substance was obtained from

a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours
5 and 1N hydrochloric acid (25 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained pale-yellow oily substance was crystallized from hexane to give [2-(3-{3-tert-butyl-1-[5-(trifluoromethyl)-2-
10 pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-ethylphenyl]acetic acid (370 mg, yield 49%) as colorless crystals. melting point: 98-99°C.

Example 348

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (330 mg), methyl (3-hydroxy-2-methyl-4-pyridinyl)acetate (175 mg), tributylphosphine (538 μ l) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (488 mg) at room temperature, and the mixture was stirred at 50°C for 2 hours.
20 The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (15 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at room temperature for 30 minutes. 1N Hydrochloric acid (15 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica
25 gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with methanol-ethyl acetate (1:3, volume ratio). The obtained a yellow oily substance was crystallized from hexane to give [3-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-
30 methyl-4-pyridinyl]acetic acid (53.0 mg, yield 11%) as pale-
35

yellow crystals. melting point: 78-79°C.

Example 349

To a mixture of 2-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-ethanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (315 mg), tributylphosphine (540 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}ethoxy-3-methoxyphenyl)acetic acid (535 mg, yield 86%) as colorless crystals. The crystals were recrystallized from ethyl acetate-hexane. melting point: 165-166°C.

Example 350

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (230 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (610 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-(3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetate (520 mg, yield 86%) was obtained as a

colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 0.87 (6H, t, J=7.6 Hz), 1.69-1.79 (4H, m), 2.02-2.09 (2H, m), 2.57-2.67 (3H, m), 3.68 (3H, s), 3.69 (2H, s), 3.85 (3H, s), 4.06 (2H, t, J=6.4 Hz), 6.82-6.87 (2H, m), 7.01 (1H, t, J=8.0 Hz), 7.83-7.84 (2H, m), 8.25 (1H, s), 8.38-8.39 (1H, m).

Example 351

A mixture of methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (500 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol (7 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (7 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (430 mg, yield 88%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 94-95°C.

Example 352

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (210 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (610 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl)acetate (380 mg, yield 65%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane

(1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 0.87 (6H, t, J=7.2 Hz), 1.68-1.78 (4H, m), 2.07-2.13 (2H, m), 2.30 (3H, s), 2.57-2.70 (3H, m), 3.68 (2H, s), 3.68 (3H, s), 3.87 (2H, t, J=6.4 Hz), 6.99 (1H, t, J=7.6 Hz), 7.09-7.11 (2H, m), 7.84 (2H, m), 8.24 (1H, s), 8.38-8.39 (1H, m).

Example 353

A mixture of methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl) acetate (360 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol (7 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (7 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl) acetic acid (310 mg, yield 89%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 120-121°C.

Example 354

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (3-ethyl-2-hydroxyphenyl) acetate (230 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (610 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl) acetate (280 mg, yield 47%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). ¹H-NMR (CDCl₃) δ: 0.88 (6H, t, J=7.6 Hz), 1.23 (3H, t, J=7.6

Hz), 1.69-1.79 (4H, m), 2.08-2.15 (2H, m), 2.58-2.70 (5H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.84 (2H, m), 8.24 (1H, s), 8.39 (1H, m).

⁵ Example 355

A mixture of methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (220 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room ¹⁰ temperature for 4 hours. 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-¹⁵ pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (180 mg, yield 84%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 123°C.

Example 356

²⁰ To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (410 mg), methyl (2-hydroxy-3-isopropylphenyl)acetate (280 mg), tributylphosphine (560 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (700 mg) at room temperature, and ²⁵ the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl [3-isopropyl-2-(3-(3-isopropyl-1-³⁰ [5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (430 mg, yield 66%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.22 (6H, d, J=6.8 Hz), 1.36 (6H, d, J=7.2 Hz), 2.12-2.18 (2H, m), 2.74 (2H, t, J=8.0 Hz), 3.04-3.10 (1H,

m), 3.25-3.31 (1H, m), 3.69 (2H, s), 3.69 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.06-7.11 (2H, m), 7.19-7.21 (1H, m), 7.95 (1H, dd, J=8.8, 2.4 Hz), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

5 Example 357

A mixture of methyl [3-isopropyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (420 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol 10 (5 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration 15 to give [3-isopropyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (310 mg, yield 76%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 108-109°C.

Example 358

20 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (410 mg), methyl (2-hydroxy-3-isopropylphenyl)acetate (280 mg), tributylphosphine (560 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (700 mg) at room temperature, and 25 the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl [3-isopropyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4- 30 yl}propoxy)phenyl]acetate (430 mg, yield 66%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.04 (3H, t, J=7.2 Hz), 1.21 (6H, d, J=7.2 Hz), 1.73-1.81 (2H, m), 2.11-2.17 (2H, m), 2.66 (2H, t, J=8.0

Hz), 2.71 (2H, t, J=8.0 Hz), 3.25-3.31 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.85 (2H, t, J=6.4 Hz), 7.06-7.11 (2H, m), 7.20 (1H, dd, J=7.0, 2.4 Hz), 7.96 (1H, dd, J=8.4, 2.4 Hz), 8.02 (1H, d, J=8.4 Hz), 8.34 (1H, s), 8.61 (1H, m).

⁵ Example 359

A mixture of methyl [3-isopropyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (420 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [3-isopropyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (350 mg, yield 86%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 102-103°C.

Example 360

To a mixture of 3-{3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (190 mg), tributylphosphine (410 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (520 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl [2-(3-{3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (440 mg, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

¹H-NMR ($CDCl_3$) δ : 1.33 (6H, d, J=6.8 Hz), 2.05-2.12 (2H, m), 2.68-2.72 (2H, m), 3.01-3.08 (1H, m), 3.67 (3H, s), 3.69 (2H,

s), 3.83 (3H, s), 4.07 (2H, t, J=6.4 Hz), 6.82-6.86 (2H, m), 6.98-7.02 (1H, m), 7.31 (1H, dd, J=8.0, 4.8 Hz), 8.01 (1H, s), 8.14 (1H, dd, J=8.0, 1.6 Hz), 8.59 (1H, dd, J=4.8, 1.6 Hz).

Example 361

5 A mixture of methyl [2-(3-{3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (420 mg), 1N aqueous sodium hydroxide solution (6 ml), tetrahydrofuran (5 ml) and methanol (6 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric
10 acid (6 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-
15 yl}propoxy)-3-methoxyphenyl]acetic acid (370 mg, yield 91%) as a colorless oil.

1H -NMR ($CDCl_3$) δ : 1.29 (6H, d, J=6.8 Hz), 2.15-2.22 (2H, m), 2.65 (2H, t, J=7.2 Hz), 2.96-3.03 (1H, m), 3.70 (2H, s), 3.83 (3H, s), 4.05-4.09 (2H, m), 6.82-6.86 (2H, m), 7.00 (1H, t,
20 J=8.0 Hz), 7.36 (1H, dd, J=7.6, 4.8 Hz), 8.07 (1H, s), 8.18 (1H, dd, J=7.6, 1.6 Hz), 8.57 (1H, dd, J=4.8, 1.6 Hz).

Example 362

To a mixture of 3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (190 mg), tributylphosphine (410 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (520 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the
30 insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (400 mg, yield 85%) was obtained as a
35 colorless oil from a fraction eluted with ethyl acetate-hexane

(1:9, volume ratio).

¹H-NMR (CDCl₃) δ: 1.35 (6H, d, J=6.8 Hz), 2.05-2.12 (2H, m), 2.68-2.72 (2H, m), 3.03-3.10 (1H, m), 3.67 (3H, s), 3.69 (2H, s), 3.85 (3H, s), 4.07 (2H, t, J=6.4 Hz), 6.83-6.86 (2H, m), 5 6.99-7.03 (1H, m), 7.28 (1H, d, J=5.2 Hz), 8.16 (1H, s), 8.31 (1H, s), 8.50 (1H, d, J=5.2 Hz).

Example 363

A mixture of methyl [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (310 mg), 1N aqueous sodium hydroxide solution (6 ml), tetrahydrofuran (5 ml) and methanol (6 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (6 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (260 mg, yield 86%). melting point: 127-128°C.

Example 364

To a mixture of 3-{3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (190 mg), tributylphosphine (410 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (520 mg) at room temperature, and the mixture was stirred overnight at 65°C. The reaction solution was concentrated. Isopropyl ether was added and the insoluble material was filtered off. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl [2-(3-{3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (390 mg, yield 83%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

³⁵ ¹H-NMR (CDCl₃) δ: 1.34 (6H, d, J=6.8 Hz), 2.05-2.12 (2H, m),

2.68-2.72 (2H, m), 3.03-3.09 (1H, m), 3.68 (3H, s), 3.69 (2H, s), 3.86 (3H, s), 4.07 (2H, t, J=6.4 Hz), 6.83-6.87 (2H, m), 6.99-7.03 (1H, m), 7.44 (1H, d, J=7.6 Hz), 7.88-7.92 (1H, m), 8.13 (1H, d, J=8.4 Hz), 8.35 (1H, s).

5 Example 365

A mixture of methyl [2-(3-{3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (360 mg), 1N aqueous sodium hydroxide solution (6 ml), tetrahydrofuran (5 ml) and methanol (6 ml)
10 was stirred at room temperature for 4 hours. 1N Hydrochloric acid (6 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[6-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (290 mg, yield 83%).
melting point: 95-97°C.

Example 366

To a mixture of 3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (215 mg), tributylphosphine (454 μ l) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (460 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:10, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (6 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (6 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography. The fraction eluted with ethyl acetate-

hexane (1:1, volume ratio) was concentrated and crystallized from ethyl acetate-hexane to give [2-(3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (261 mg, yield 58%) as colorless
5 crystals. melting point: 131-132°C.

Example 367

To a mixture of 3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (350 mg), methyl (2-hydroxy-3-methylphenyl)acetate (202 mg),
10 tributylphosphine (558 µl) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (565 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily
15 substance was obtained from a fraction eluted with ethyl acetate-hexane (1:10, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (6 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (6 ml) was added,
20 and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography. The fraction eluted with ethyl acetate-hexane (1:1, volume ratio) was concentrated, and crystallized
25 from ethyl acetate-hexane to give [2-(3-{3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (219 mg, yield 43%) as colorless crystals. melting point: 96-97°C.

Example 368

30 To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-yl]-1-propanol (200 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (120 mg), tributylphosphine (240 mg) and tetrahydrofuran (40 ml), was added 1,1'-azodicarbonyldipiperidine (300 mg) at room temperature, and
35 the mixture was stirred for 3 hours. The reaction solution was

concentrated. The precipitated crystals were removed by filtration with diethyl ether and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and an oily substance (244 mg) was obtained
5 from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (3 ml) and methanol (3 ml) was stirred at 50°C-60°C for 1 hour. The reaction mixture was poured into water and the mixture was
10 acidified with 2N hydrochloric acid. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried (MgSO_4) and concentrated. The residue was subjected to silica gel column chromatography, and (2-[3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-
15 yl]propoxy]-3-methoxyphenyl)acetic acid (210 mg, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.37 (9H, s), 2.1-2.35 (2H, m), 2.78 (2H, d, $J=7.2$ Hz), 3.73 (2H, s), 3.84 (3H, s), 4.12 (2H, t, $J=7.2$ Hz),
20 6.8-7.05 (3H, m), 7.86 (2H, d, $J=1.4$ Hz), 8.33 (1H, br s), 8.36 (1H, t, $J=1.4$ Hz).

Example 369

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-yl]-1-propanol (250 mg), methyl (2-hydroxy-3-methylphenyl)acetate (200 mg), tributylphosphine (450 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (560 mg) at room temperature, and the mixture was stirred at 100°C for 6 hours. The reaction solution was concentrated. The precipitated crystals were
30 filtrated with diethyl ether and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and an oily substance (250 mg) was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and
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methanol (2 ml) was stirred at 50°C-60°C for 1 hour. The reaction mixture was poured into water and the mixture was acidified with 2N hydrochloric acid. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with
5 saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and (2-[3-[1-(5-bromo-2-pyridinyl)-3-tert-butyl-1H-pyrazol-4-yl]propoxy]-3-methylphenyl)acetic acid (190 mg, yield 53%) was obtained as crystals from a fraction eluted with ethyl
10 acetate-hexane (1:2, volume ratio). The crystals were recrystallized from diethyl ether-hexane. melting point: 62-63°C.

Example 370

To a mixture of 3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-
15 1H-pyrazol-4-yl]-1-propanol (240 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (190 mg), tributylphosphine (320 mg) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (400 mg) at room temperature, and the mixture was stirred for 15 hours. The reaction solution
20 was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and ethanol (2 ml) was stirred at 50°C for 30 minutes and 1N hydrochloric
25 acid (2 ml) and water were added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and (2-(3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-
30 yl]propoxy)-3-methoxyphenyl)acetic acid (230 mg, yield 61%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from hexane-diethyl ether to give colorless
35 prism crystals. melting point: 87-88°C.

Example 371

To a mixture of 3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-yl]-1-propanol (240 mg), methyl (2-hydroxy-3-methylphenyl)acetate (180 mg), tributylphosphine (640 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature, and the mixture was heated under reflux for 4 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (0:100 to 5:95, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and ethanol (2 ml) was stirred at 50°C for 30 minutes. 1N Hydrochloric acid (2 ml) and water were added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give (2-{3-[3-tert-butyl-1-(5-chloropyridin-2-yl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl)acetic acid (150 mg, yield 42%) as colorless crystals. The crystals were recrystallized from hexane-diethyl ether to give colorless prism crystals. melting point: 112-113°C.

Example 372

To a mixture of [3-methyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]methanol (2.30 g), ethyl 3-(4-hydroxyphenyl)propionate (2.58 g), tributylphosphine (4.93 g) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (6.16 g) at room temperature, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (10:90, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (15 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (15 ml) and water were added, and the mixture was extracted

with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give 3-[4-[3-methyl-1-(2-pyridinyl)-1H-pyrazol-4-ylmethoxy]phenyl]propionic acid (3.05 g, yield 74%) as colorless crystals. The crystals were recrystallized from ethanol-water. melting point: 129-130°C.

Example 373

To a mixture of [3-methyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]methanol (3.14 g), methyl (4-hydroxyphenyl)acetate (3.00 g), tributylphosphine (6.71 g) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (8.36 g) at room temperature, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (10:90, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (20 ml) and water were added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated to give {4-[3-methyl-1-(2-pyridinyl)-1H-pyrazol-4-ylmethoxy]phenyl}acetic acid (3.15 g, yield 59%) as colorless crystals. The crystals were recrystallized from ethanol-water. melting point: 161-162°C.

Example 374

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(3-hydroxy-4-methylphenoxy)-2-methylpropanonate (455 mg), tributylphosphine (792 μ L) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature, and the mixture was stirred for 3 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature 5 for 3 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a 10 fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.20 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the residue and water (50 ml) 15 was added calcium chloride (127 mg) dissolved in a small amount of water and the mixture was stirred at room temperature for 3 hours. The resulting white precipitates were collected by filtration to give calcium 2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4- 20 methylphenoxy]-2-methylpropanoate (521 mg, yield 62%) as amorphous.

1H -NMR (DMSO-d₆) δ : 1.34 (3H, t, $J=7.0$ Hz), 1.38 (6H, s), 1.92-2.09 (2H, m), 2.04 (3H, s), 2.46-2.61 (2H, m), 3.85-3.97 (2H, m), 4.31 (2H, q, $J=7.0$ Hz), 6.31-6.39 (1H, m), 6.41-6.47 (1H, m), 6.85 (1H, d, $J=8.0$ Hz), 7.81 (1H, d, $J=8.8$ Hz), 8.22-8.30 (1H, m), 8.34 (1H, s), 8.70-8.76 (1H, m).

Example 375

To a mixture of 3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 2-(3-hydroxy-4-methylphenoxy)-2-methylpropanoate (458 mg), tributylphosphine (797 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected 35 to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature 5 for 3 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. A mixture of the residue, 1N aqueous sodium hydroxide solution (1.50 ml), tetrahydrofuran (25 ml) and 10 ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the residue and water (50 ml) was added calcium chloride (158 mg) dissolved in a small amount of water and the mixture was stirred at room temperature for 1 hour. The resulting white precipitates were 15 collected by filtration to give calcium 2-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methylphenoxy]-2-methylpropanoate (647 mg, yield 77%) as amorphous.

1H -NMR (DMSO-d₆) δ : 1.26 (6H, d, J=6.8 Hz), 1.39 (6H, s), 1.92-20 2.12 (2H, m), 2.05 (3H, s), 2.56-2.72 (2H, m), 2.92-3.10 (1H, m), 3.87-4.02 (2H, m), 6.32-6.41 (1H, m), 6.43-6.49 (1H, m), 6.85 (1H, d, J=8.4 Hz), 7.98 (1H, d, J=8.8 Hz), 8.29 (1H, dd, J=2.2, 8.8 Hz), 8.39 (1H, s), 8.74-8.82 (1H, m).

Example 376

25 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(3-hydroxy-4-methoxyphenoxy)-2-methylpropanoate (488 mg), tributylphosphine (797 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room 30 temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 35 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran

(25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained pale-yellow solid was recrystallized from diisopropyl ether-hexane to give 2-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenoxy]-2-methylpropanoic acid (610 mg, yield 73%) as colorless crystals. melting point: 106-107°C.

10 Example 377

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(4-ethyl-3-hydroxyphenoxy)-2-methylpropanoate (484 mg), tributylphosphine (797 μ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature, and the mixture was stirred for 1.5 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (3:37, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried ($MgSO_4$) and concentrated. The obtained white solid was recrystallized from diisopropyl ether-hexane to give 2-[4-ethyl-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropanoic acid (565 mg, yield 68%) as colorless crystals. melting point: 115-116°C.

Example 378

A mixture of 2-(3-{3-isopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxybenzaldehyde (0.4 g), tetrahydrofuran (4 ml), methyl

methylthiomethyl sulfoxide (0.14 ml) and sodium hydroxide (0.04 g) was reacted for about 5 hours under reflux. The mixture was cooled to room temperature and water was added. The mixture was extracted with ethyl acetate. The aqueous 5 layer was further extracted with ethyl acetate. The organic layers were combined and washed twice with water. The organic layer was concentrated and a mixture of the residue, ethanol (8 ml) and conc. hydrochloric acid (0.74 ml) was stirred at 80°C for about 14 hours. The mixture was cooled to room 10 temperature and 1N aqueous sodium hydroxide solution (10.7 ml) and ethanol (20 ml) were added. The mixture was stirred at about 70°C for 1 hour. The mixture was cooled to room temperature and water (10 ml) and toluene (10 ml) were added. 1N Aqueous sodium hydroxide solution (10 ml) was added to the 15 organic layer and partitioned. The aqueous layers were combined and conc. hydrochloric acid was dropwise added. The mixture was adjusted to pH 2.0 and extracted with ethyl acetate. The organic layer was washed twice with water, and heptane (2 ml) was added. The mixture was stirred at room 20 temperature for about 0.5 hour. The precipitated crystals were collected by filtration and washed with heptane to give [2-(3-{3-isopropyl-1-(5-trifluoromethylpyridin-2-yl)-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (0.30 g, yield 70.3%) as pale-yellow white crystals.

25 ¹H-NMR (CDCl₃) δ: 1.32 (6H, d, J=6.9 Hz), 2.1-2.2 (2H, m), 2.6-2.7 (2H, m), 3.0-3.1 (1H, m), 3.71 (2H, s), 3.84 (3H, s), 4.0-4.2 (2H, m), 6.8-7.1 (3H, m), 7.90 (1H, dd, J=8.7, 2.2 Hz), 8.04 (1H, d, J=8.7 Hz), 8.36 (1H, s), 8.5-8.6 (1H, m).

Example 379

30 A mixture of 2-(3-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl)propoxy)-3-methoxybenzaldehyde (585 mg), tetrahydrofuran (5.85 ml), methyl methylthiomethyl sulfoxide (0.193 ml) and sodium hydroxide (0.049 g) was stirred for about 5 hours under 35 reflux. The mixture was cooled to room temperature and water

was added. The mixture was extracted with ethyl acetate and the aqueous layer was further extracted with ethyl acetate. The organic layers were combined, washed with water, and the organic layer was concentrated. A mixture of the residue,
⁵ ethanol (10.5 ml) and 4N hydrochloric acid-ethyl acetate (3.05 ml) was stirred at about 80°C for about 1 hour. The mixture was cooled to room temperature. Saturated aqueous sodium hydrogen carbonate was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water,
¹⁰ dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give ethyl [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetate (537 mg, yield 82%) as an oily substance.

¹⁵ ¹H-NMR (CDCl₃) δ: 0.8-0.9 (6H, m), 1.2-1.3 (3H, m), 1.6-1.8 (4H, m), 2.0-2.1 (2H, m), 2.6-2.7 (3H, m), 3.68 (2H, s), 3.85 (3H, s), 4.0-4.2 (2H, m), 6.8-6.9 (2H, m), 7.0-7.1 (1H, m), 7.94 (1H, dd, J=8.7, 2.2 Hz), 8.04 (1H, d, J=8.7 Hz), 8.33 (1H, s), 8.6-8.7 (1H, m).

²⁰ **Preparation Example 1** (Production of capsules)

1) Compound of Example 1	30 mg
2) Finely divided cellulose	10 mg
3) Lactose	19 mg
4) Magnesium stearate	1 mg
²⁵ Total	60 mg

1), 2), 3) and 4) are admixed and filled into a gelatin capsule.

Preparation Example 2 (Production of tablets)

30	1) Compound of Example 1	30 g
	2) Lactose	50 g
	3) Corn starch	15 g
	4) Carboxymethylcellulose calcium	44 g
	5) Magnesium stearate	1 g
³⁵	1000 tablets	140 g

The whole amounts of 1), 2) and 3) and 30 g of 4) are kneaded together with water and the mixture, after vacuum drying, is granulated. The granular mixture is admixed with 14 g of 4) and 1 g of 5) and the resulting mixture is tableted 5 using a tabletting machine, to give 1000 tablets each containing 30 mg of compound of Example 1.

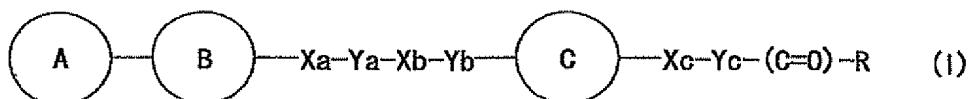
Industrial Applicability

The compound of the present invention is superior in a 10 hypoglycemic action, a hypolipidemic action, a hypoinsulinemic action, insulin resistance-improving action, insulin sensitivity enhancing action and retinoid-related receptor function regulating activity, and can be used as an agent for the prophylaxis or treatment of diabetes (e.g., type 1 15 diabetes, type 2 diabetes, gestational diabetes); an agent for the prophylaxis or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-high-density-lipoproteinemia, postprandial hyperlipemia); an agent for improving insulin resistance; an agent for enhancing insulin 20 sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance [IGT]; and an agent for preventing progress from impaired glucose tolerance to diabetes.

This application is based on patent application Nos. 25 2002-151405, 2002-287161 and 2003-16748 filed in Japan, the contents of which are hereby incorporated by reference.

CLAIMS

1. A compound represented by the formula



5 wherein

ring A is a ring optionally having 1 to 3 substituents;
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

10 are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

15 Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Yb and Yc

20 are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

25 R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶ form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), provided that,

30 (1) when the 1,2-azole ring represented by ring B is

pyrazole, ring C is not thiadiazole or oxadiazole;
(2) when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone; and
5 (3) when the 1,2-azole ring represented by ring B is pyrazole and X_a and X_b are each a bond, ring C is not a benzene ring,
or a salt thereof.

10 2. The compound of claim 1, wherein the ring represented by ring A is an aromatic ring.

3. The compound of claim 2, wherein the aromatic ring is a benzene ring, a pyridine ring or a pyridazine ring.

15 4. The compound of claim 1, wherein the 1,2-azole ring represented by ring B is pyrazole.
5. The compound of claim 1, wherein the substituent that ring
20 B is optionally further having is a hydrocarbon group.

6. The compound of claim 1, wherein the substituent that ring B is optionally further having is an alkoxy group.

25 7. The compound of claim 1, wherein Y_a is C₁₋₆ alkylene or C₂₋₆ alkenylene.

8. The compound of claim 1, wherein X_b is -O-, -S-, -SO-,
-SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a
30 hydrogen atom or an optionally substituted hydrocarbon group,
R² is a hydrogen atom or a hydroxy-protecting group, and R³ is
a hydrogen atom, an optionally substituted hydrocarbon group
or an amino-protecting group).

35 9. The compound of claim 1, wherein the monocyclic aromatic

ring represented by ring C is a benzene ring.

10. The compound of claim 1, wherein the monocyclic aromatic ring represented by ring C is pyrazole.

5

11. The compound of claim 1, wherein R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group).

12. The compound of claim 1, wherein Xa is a bond.

10

13. The compound of claim 1, wherein Xb is -O-.

14. The compound of claim 1, wherein Yb is a bond.

15

15. The compound of claim 1, wherein Xc is a bond or -O-.

16. The compound of claim 1, wherein Yc is C₁₋₆ alkylene or C₂₋₆ alkenylene.

20

17. The compound of claim 1, which is 3-[1-phenyl-3-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)-1H-pyrazol-5-yl]propionic acid;

2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid;

25

3-[2-ethoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid;

3-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid;

[1-phenyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-4-yl]acetic acid;

30

[2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid;

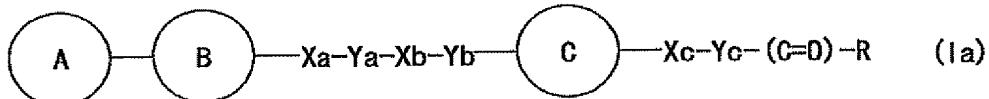
[2-(3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-3-methoxyphenyl]acetic acid;

35

(2-{3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-

yl]propoxy}-3-methoxyphenyl)acetic acid;
[3-ethyl-2-(3-(3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid;
[2-(3-(3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)propoxy)-3-methoxyphenyl]acetic acid;
[3-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid;
[1-ethyl-5-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-4-yl]acetic
acid;
[1-ethyl-5-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-4-yl]acetic acid;
(2-(3-[1-(5-bromo-2-pyridinyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy)-3-methoxyphenyl)acetic acid; or
[2-(3-tert-butyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl)propoxy)-3-methylphenyl]acetic acid.

18. A prodrug of the compound of claim 1 or a salt thereof.
20 19. A pharmaceutical composition comprising the compound of
claim 1 or a salt thereof or a prodrug thereof.
25 20. An agent for the prophylaxis or treatment of diabetes,
which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;
ring B is a 1,2-azole ring optionally further having 1 to 3
substituents;

X_a, X_b and X_c

are the same or different and each is a bond, -O-,
-S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³-

or $-NR^3CO-$ (R^1 is a hydrogen atom or an optionally substituted hydrocarbon group, R^2 is a hydrogen atom or a hydroxy-protecting group, and R^3 is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

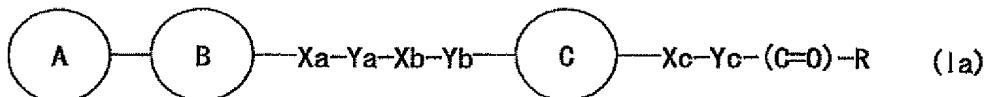
Yb and Yc

are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

R represents $-OR^4$ (R^4 is a hydrogen atom or an optionally substituted hydrocarbon group) or $-NR^5R^6$ (R^5 and R^6 are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R^5 and R^6 form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),
or a salt thereof or a prodrug thereof.

21. An agent for the prophylaxis or treatment of hyperlipidemia, which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond, $-O-$,

-S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

5

Y_a is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Y_b and Y_c

10

are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

15

R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶

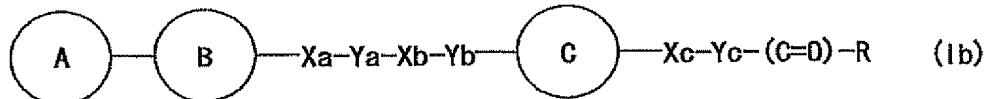
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form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),

or a salt thereof or a prodrug thereof.

22. An agent for the prophylaxis or treatment of

arteriosclerosis, which comprises a compound represented by the formula



wherein

30 ring A is a ring optionally having 1 to 3 substituents;
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

X_a, X_b and X_c

are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Yb and Yc

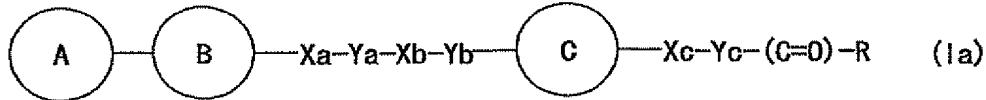
are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶ form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), provided that, when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone,

or a salt thereof or a prodrug thereof.

23. An agent for the prophylaxis or treatment of impaired glucose tolerance, which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;
 ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

X_a, X_b and X_c

5 are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

10 Y_a is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Y_b and Y_c

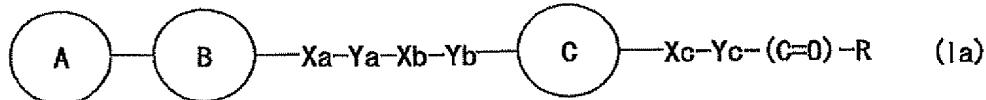
15 are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

20 R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶ form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),

25 or a salt thereof or a prodrug thereof.

24. A retinoid-related receptor function regulating agent,
 30 which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

5 are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, 10 an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Yb and Yc

15 are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

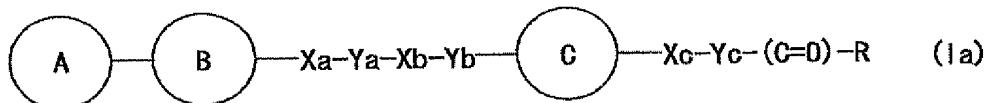
20 R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶ 25 form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof.

25. The agent of claim 24, which is a peroxisome proliferator-
30 activated receptor ligand.

26. The agent of claim 24, which is a retinoid X receptor ligand.

35 27. An insulin resistance improving agent, which comprises a

compound represented by the formula



wherein

5 ring A is a ring optionally having 1 to 3 substituents;
 ring B is a 1,2-azole ring optionally further having 1 to 3
 substituents;

X_a , X_b and X_c

10 are the same or different and each is a bond, $-\text{O}-$,
 $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{CO}-$, $-\text{CS}-$, $-\text{CR}^1(\text{OR}^2)-$, $-\text{NR}^3-$, $-\text{CONR}^3-$
 or $-\text{NR}^3\text{CO}-$ (R^1 is a hydrogen atom or an optionally
 substituted hydrocarbon group, R^2 is a hydrogen atom or
 a hydroxy-protecting group, and R^3 is a hydrogen atom,
 an optionally substituted hydrocarbon group or an
 15 amino-protecting group);

Y_a is a divalent aliphatic hydrocarbon residue having 1
 to 20 carbon atoms;

Y_b and Y_c

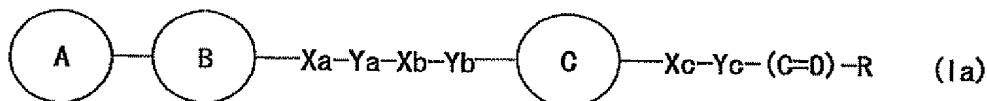
20 are the same or different and each is a bond or a
 divalent aliphatic hydrocarbon residue having 1 to 20
 carbon atoms;

ring C is a monocyclic aromatic ring optionally further
 having 1 to 3 substituents; and

25 R represents $-\text{OR}^4$ (R^4 is a hydrogen atom or an optionally
 substituted hydrocarbon group) or $-\text{NR}^5\text{R}^6$ (R^5 and R^6 are
 the same or different and each is a hydrogen atom, an
 optionally substituted hydrocarbon group or an
 optionally substituted heterocyclic group, or R^5 and R^6
 form, together with the adjacent nitrogen atom, an
 30 optionally substituted heterocyclic ring),
 or a salt thereof or a prodrug thereof.

28. A method for the prophylaxis or treatment of diabetes in a

mammal in need thereof, which comprises administering to the mammal a compound represented by the formula



⁵ wherein

ring A is a ring optionally having 1 to 3 substituents;
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

¹⁰ are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or a hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

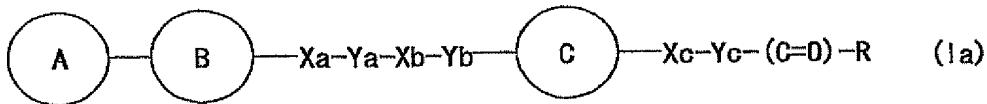
Yb and Yc

²⁰ are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents; and

²⁵ R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R⁵ and R⁶ form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),
³⁰ or a salt thereof or a prodrug thereof.

29. Use of a compound represented by the formula



wherein

5 ring A is a ring optionally having 1 to 3 substituents;
 ring B is a 1,2-azole ring optionally further having 1 to 3
 substituents;

X_a, X_b and X_c

10 are the same or different and each is a bond, -O-,
 -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³-
 or -NR³CO- (R¹ is a hydrogen atom or an optionally
 substituted hydrocarbon group, R² is a hydrogen atom or
 a hydroxy-protecting group, and R³ is a hydrogen atom,
 an optionally substituted hydrocarbon group or an
 15 amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1
 to 20 carbon atoms;

Yb and Yc

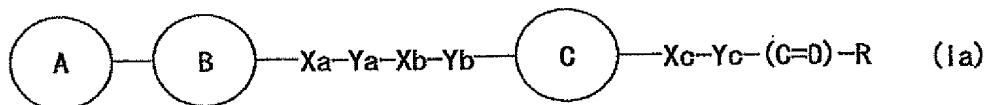
20 are the same or different and each is a bond or a
 divalent aliphatic hydrocarbon residue having 1 to 20
 carbon atoms;

ring C is a monocyclic aromatic ring optionally further
 having 1 to 3 substituents; and

25 R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally
 substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are
 the same or different and each is a hydrogen atom, an
 optionally substituted hydrocarbon group or an
 optionally substituted heterocyclic group, or R⁵ and R⁶
 form, together with the adjacent nitrogen atom, an
 30 optionally substituted heterocyclic ring),

or a salt thereof or a prodrug thereof, for the production of
 an agent for the prophylaxis or treatment of diabetes.

30. A GPR40 receptor function modulator comprising a compound represented by the formula



5

wherein

ring A is a ring optionally having 1 to 3 substituents;
ring B is 1,2-azole ring optionally further having 1 to 3 substituents;

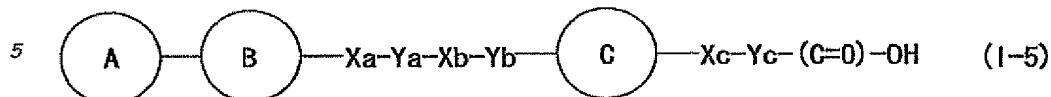
10 Xa, Xb and Xc
are the same or different and each is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CS-, -CR¹(OR²)-, -NR³-, -CONR³- or -NR³CO- (R¹ is a hydrogen atom or an optionally substituted hydrocarbon group, R² is a hydrogen atom or 15 hydroxy-protecting group, and R³ is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

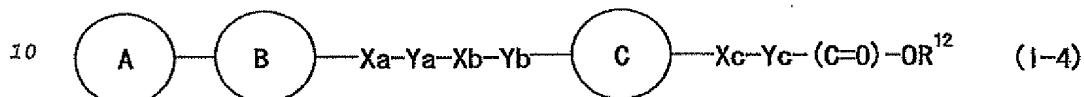
20 Yb and Yc
are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further 25 having 1 to 3 substituents; and
R represents -OR⁴ (R⁴ is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR⁵R⁶ (R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an 30 optionally substituted heterocyclic group, or R⁵ and R⁶ form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),
or a salt thereof or a prodrug thereof.

31. A production method of a compound represented by the formula

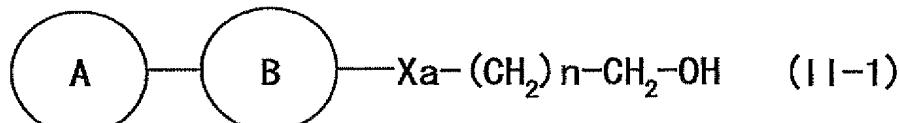


wherein the symbols in the formula are as defined in claim 1, or a salt thereof, which comprises subjecting a compound represented by the formula

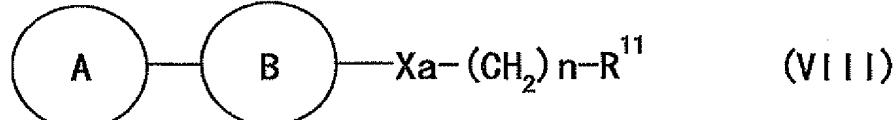


wherein R¹² is an optionally substituted hydrocarbon group and other symbols are as defined above, or a salt thereof to a hydrolysis reaction.

15 32. A production method of a compound represented by the formula

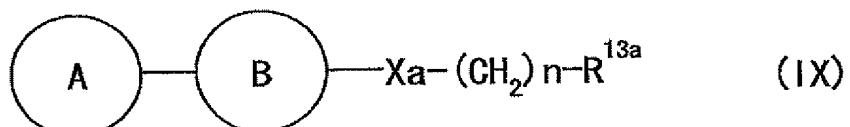


wherein n is an integer of 0 to 5 and other symbols are as defined in claim 1, or a salt thereof, which comprises subjecting a compound represented by the formula



wherein R¹¹ is CHO or COOR¹³ (R¹³ is an alkyl group having 1-6 carbon atoms), and other symbols are as defined above, or a salt thereof to a reduction reaction.

33. A compound represented by the formula



wherein n is an integer of 0 to 5, R^{13a} is CH_2OH , CHO or COOR^{14}

5 (R^{14} is an alkyl group having 1-6 carbon atoms), and other symbols are as defined in claim 1, or a salt thereof.

SEQUENCE LISTING

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 03/06389

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/12	C07D261/08	C07D401/04	C07D413/12	A61K31/4155
A61K31/415	A61K31/42	A61K31/422	A61K31/4439	C07D231/14
C07D231/20	C07D231/22	C07D401/14	C07D403/04	C07D403/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	EP 1 216 980 A (EISAI CO LTD) 26 June 2002 (2002-06-26) page 247 -page 248; claim 1 page 3, line 21 - line 24 & WO 01 25181 A (EISAI CO LTD) 12 April 2001 (2001-04-12) ----	1-17, 19-31
X	EP 0 513 580 A (BASF AG) 19 November 1992 (1992-11-19) page 185 -page 187; claim 1 page 7; line 5, the compounds of general formula (IV) ----	1-17, 19-31
X	EP 0 378 755 A (BASF AG) 25 July 1990 (1990-07-25) page 39; claim 3 ----	1-16, 24-27, 30
X	EP 0 378 755 A (BASF AG) 25 July 1990 (1990-07-25) page 39; claim 3 ----	24-27, 30
		-/-

 Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

10 September 2003

24/09/2003

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/06389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 35669 A (BASF AG ;GROTE THOMAS (DE); KIRSTGEN REINHARD (DE); MUELLER BERND) 14 November 1996 (1996-11-14) page 202; claim 1 --	1-16, 24-27, 30
X	EP 0 581 095 A (BASF AG) 2 February 1994 (1994-02-02) page 74; claim 12 --	1-16, 24-27, 30
X	EP 0 525 516 A (BASF AG) 3 February 1993 (1993-02-03) page 116 -page 117; claim 1 --	1-16, 24-27, 30
X	EP 0 558 062 A (ONO PHARMACEUTICAL CO) 1 September 1993 (1993-09-01) page 92 -page 96; claim 1 page 112; claims 20,21 --	1-16, 19, 22-27, 30, 31
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

10 September 2003

Name and mailing address of the ISA

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Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 03/06389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 442 448 A (SQUIBB BRISTOL MYERS CO) 21 August 1991 (1991-08-21) cited in the application page 47; claim 2 page 37 -page 38; examples 26,27	20-27,30
P,X	WO 03 015771 A (LION BIOSCIENCE AG) 27 February 2003 (2003-02-27) page 34 -page 37; claims 1-4,6,7	1-16, 19-27
X	WO 00 64876 A (MCGEEHAN GERARD M ;MORRIS ROBERT (US); ZHANG LITAO (US); BOBKOV MAR) 2 November 2000 (2000-11-02) cited in the application the whole document	1-17, 19-31
Y	WO 01 38325 A (MOMOSE YU ;KIMURA HIROYUKI (JP); ODAKA HIROYUKI (JP); MAEKAWA TSUY) 31 May 2001 (2001-05-31) cited in the application the whole document	1-31
Y	WO 01 00603 A (SIERRA MICHAEL LAWRENCE ;GELLIBERT FRANCOISE JEANNE (FR); GLAXO GR) 4 January 2001 (2001-01-04) cited in the application the whole document	1-31
A	WO 97 31907 A (CALLAGHAN JOHN MARK O ;GLAXO GROUP LTD (GB); COBB JEFFREY EDMOND () 4 September 1997 (1997-09-04) cited in the application the whole document	1-31
X	US 4 146 721 A (RAINER GEORG) 27 March 1979 (1979-03-27) the whole document and, in particular, example 54(f) -(j)	32,33
X	BARREIRO E J ET AL: "Synthesis of Pryzole Derivatives as Potential Bioisosteres of Thromboxane-Synthetase Inhibitors" JOURNAL OF HETERO CYCLIC CHEMISTRY, vol. 29, 1992, pages 407-411, XP002253754 page 408, the compounds 6, 9-11 and 14-16	32,33
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 03/06389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4424469 XP002253755 abstract & CHEM. HETEROCYCL. COMPD. (ENGL. TRANSL.), vol. 20, no. 1, 1984, page 114 ____	33
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 649155 XP002253756 abstract & J. CHEM. SOC., PERKIN TRANS. 1, 1974, pages 1871-1875, ____	33
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 7211617 XP002253757 abstract & HETEROCYCLES , vol. 40, no. 2, 1995, pages 515-520, ____	33

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/JP 03/06389**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-16 (all partly), 18, 19-31 (all partly), 32, 33 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16 (all partly), 18, 19-31 (all partly), 32, 33

Present compound claims 1-16, 24-27 and 30 relate to an extremely large number of possible compounds (see, in particular, the non-limitative (open-ended) expressions, such as "a ring optionally having 1 to 3 substituents", "optionally substituted hydrocarbon group", "hydroxy-protecting group", "optionally substituted heterocyclic ring"...etc.). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of claims 1-16 which appear to be supported and disclosed, namely those parts relating to the compounds wherein
the ring A is an (optionally substituted) benzene, pyridine, or pyridazine ring (cf., the present claim 3),
the ring B is either an (optionally substituted) pyrazol-4-yl or isoxazol-5-yl (4-yl and 5-yl in respect of the group -Xa-Ya-Xb-Yb),
the groups Xa and Yb represent bonds (cf., the present claims 12 and 14),
the group Xb is either a bond or a -O- group (cf., the present claim 13),
the group Ya is C1-6 alkylene or C2-6 alkenylene (cf., the present claim 7),
the group Xc is a bond or a -O- group (cf., the present claim 15),
the group Yc is C1-6 alkylene or C2-6 alkenylene (cf., the present claim 16),
the group R represents -OR4 (cf., the present claim 11), and
the ring C is an (optionally substituted) monocyclic aromatic ring as defined in the present claim 1.

The search and the search report is therefore only complete with respect to the present claim 17.

Claims 1-16 have only been searched as far as the above-mentioned group of compounds is concerned.

It is further noted that the expression "prodrug" as used in the present claims 18-24 and 27-30 is unclear in the sense of Article 6 PCT (this expression does not comprise any information as regards the structure of the compounds concerned). It is therefore impossible to compare the claimed compounds with what is set out in the prior art. This lack of clarity is such as to render a meaningful search impossible.

Consequently, the present claim 18 has not been searched.

Claims 19-24 and 27-30 have only been searched as far as the compounds as defined hereinbefore are concerned.

Furthermore, the initial phase of the novelty-search on the intermediate compounds of the present claim 33 revealed such a vast number of novelty-destroying documents (cf., for example, the last five documents of the International Search Report) that it was impossible to determine which part of claim 33 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

For these reasons, no search has been carried out for the said claim 33 (and claim 32 which is directed to the preparation of those compounds of claim 33 wherein R13a represents CH2OH).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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